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UNIVERSITY OF CALIFORNIA, SAN DIEGO
SAN DIEGO STATE UNIVERSITY

Mediators and Moderators of Dementia Caregiver Depression and CVD Risk Outcomes
in the Pleasant Events Program

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor
of Philosophy

in

Clinical Psychology

by

Jennefer S. Ho

Committee in charge:

Professor Brent T. Mausbach, Chair
Professor Veronica Cardenas
Professor Linda Gallo
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Professor Paul Mills
Professor Kristen Wells

2016

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University of California, San Diego

San Diego State University

2016

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ABSTRACT OF THE DISSERTATION

Mediators and Moderators of Dementia Caregiver Depression and CVD Risk Outcomes
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Jennefer S. Ho

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2016

San Diego State University, 2016

Professor Brent T. Mausbach, Chair

Addressing caregiver depression is of high public health importance due to its ties with overall wellbeing, risk for cardiovascular diseases (CVD), and ability to sustain caregiving duties. To improve the impact of caregiver interventions, it is essential to understand the mechanisms through which interventions achieve reductions in depression and CVD risk, as well as the caregiving situation-related factors that may impact treatment response. The current study employed a data analytic focus on mediators and moderators of a previously completed randomized clinical trial of the Pleasant Events Program (PEP), a behavioral activation intervention. A sample of Alzheimer's Disease

spousal caregivers (N = 98 74% female) was randomized to either PEP or to a time-equivalent Informational Support control condition. PEP emphasized pleasant events scheduling and reductions in avoidance behaviors (i.e., lack of engagement in activities) in the context of ongoing caregiver responsibilities; the Informational Support intervention emphasized supportive listening and providing information. Participants were assessed at baseline and at 6-weeks. Co-primary outcomes were depression as measured by the Center for Epidemiologic Studies-Depression Scale and CVD risk marker interleukin-6. Higher levels of interleukin-6 are implicated in inflammatory processes, constituting higher risk for CVD. Multiple regression models and the Monte Carlo Method for Assessing Mediation were used to test change in pleasant events, activity restriction, and personal mastery as mediators of depression after PEP. Moreover, depression was tested as a mediator between PEP and reductions in interleukin-6. Secondly, models were used to investigate constructs measured via standardized assessments (e.g., care recipient disruptive behaviors) as moderators of PEP outcomes. The current study found that change in personal mastery, activity restriction, and pleasant activities were not significant mediators of change in depression after PEP. Moreover, changes in depression did not mediate changes in cardiovascular risk marker interleukin-6. Caregiver social support, current number of working status, vulnerability, and disruptive behaviors of care recipients did not significantly moderate treatment response. Moderators of response to PEP and mediators that account for changes in depression and CVD risk after PEP are still unknown. Future intervention studies should utilize oversampling methods to investigate mediators and moderators of post-treatment depression and interleukin-6 change.

CHAPTER 1: INTRODUCTION

Caring for a Family Member with Alzheimer's Disease

With the burgeoning aging population, increasing numbers of individuals are being diagnosed with some form of dementia. According to the International Classification of Diseases-10 (ICD-10; World Health Organization, 1992), dementia is a disease marked by a significant decline in both memory and other cognitive ability, such as judgment, thinking, planning and organizing, processing of information. There is typically preserved awareness of the environment. However, persons with dementia evidence a decline in emotional control, motivation, or change in social behavior (e.g., emotional lability and irritability). Symptoms must be present for at least 6 months to meet criteria for diagnosis. Alzheimer's Disease (AD), the most common subtype of dementia accounting for 60% - 80% of cases (Thies & Bleiler, 2013), is characterized by its progression, i.e., degenerative quality. New imaging techniques are currently being developed to aid in diagnosis of AD, including the identification of neurofibrillary tangles and amyloid plaques (Hardy & Selkoe, 2002; Shoghi-Jadid et al., 2002). Because of the degenerative nature of AD, affected individuals become increasingly impaired in their ability to carry out activities of daily living. Activities of daily living (ADLs; Katz, 1983) are defined as the daily activities that are relevant to self-care (e.g., dressing, grooming and bathing), whereas instrumental activities of daily living (IADLs) are activities relevant to independent living (e.g., handling medication and finances). Currently, over 5 million individuals in the United States have a diagnosis of AD, with over 15 million individuals serving as their unpaid caregivers (Thies & Bleiler, 2013)

Informal caregivers, i.e., non-professional caregivers (CGs) who are spouses, adult children or children-in-law, and extended family members, provide care for AD patients in various settings. Some CGs live with the care recipient in the same home, while others are living in different homes in the same neighborhood. Some care recipients have been placed into a long-term care facility, e.g., nursing home or assisted living facility. Many studies have documented the personal costs that are affiliated with becoming a CG, including limitations on one's time, loss of interpersonal connection and social activities, feeling restricted in one's own activities, and feeling watchful and "on duty." An influential longitudinal study of spousal CGs (Zarit, Todd, & Zarit, 1986) defined CG burden as "the extent to which CGs perceive that caregiving has had an adverse effect on their emotional, social, financial, physical, and spiritual functioning." The caregiving literature makes a distinction between subjective and objective CG burden. Objective burden, on the other hand, can be captured by measuring the frequency of events related to the caregiving situation (Montgomery, Gonyea, & Hooyman, 1985), e.g., the number of hours CGs spend in caregiving, the number of years, or the frequency of memory and disruptive behavior problems from the care recipient. Subjective burden, on the other hand, conforms to Zarit's definition of perceived burden from objective stressors. CGs' experience of stress and burden may vary depending on their specific caregiving situations, e.g., level of support from others (Haley, Levine, Brown, & Bartolucci, 1987), care recipient's presentation of AD, including disruptive behaviors, memory impairments, and fluctuations in mood (Schulz, O'Brien, Bookwala, & Fleissner, 1995). Severity of symptoms and their impact on CG burden may vary depending on the stage of dementia and what specific impairments and challenges the AD patient is facing (Haley

& Pardo, 1989). Common problems and concerns in AD patients include incontinence, wandering, emotional agitation, memory loss, disorientation, confusion, and disruptive behaviors (Teri, Borson, Kiyak, & Yamagishi, 1989; Teri, Larson, & Reifler, 1988). Over time, the literature suggests that CGs may experience burnout akin to what has been previously documented from work-related stress (Almberg, Grafström, & Winblad, 1997). Reaching the point of burnout and its associated mental and physical health consequences can precipitate the decision to place the care recipient into a long-term care setting, which holds implications for healthcare costs and the provision of necessary services to care recipients once they are transitioned to long-term care.

Public Health Impact of Caregiving: Depression and Physical Health Risk

With a burgeoning aging population, approximately 15 million adults in the United States are assuming informal caregiving duties for loved ones with dementia. Several studies suggest that due to the high incidence of disruptive behaviors and level of dependence on the CG in dementia (Andersen, Wittrup-Jensen, Lolk, Andersen, & Kragh-Sørensen, 2004; Langa et al., 2001), CGs of AD suffer more severe psychological and physical health consequences (Donaldson, Tarrier, & Burns, 1997; Mahoney, Regan, Katona, & Livingston, 2005) compared to CGs of persons with diabetes, the frail elderly, and even cancer (Biegel, Sales, & Schulz, 1991; Ory, Hoffman, Yee, Tennstedt, & Schulz, 1999; Schulz & Martire, 2004). AD CGs, in particular, are at heightened risk for experiencing depressive symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders 5 (APA, 2013), individuals must endorse five or more symptoms for a period of at least 2 weeks, one of which must be either depressed mood or loss of interest or pleasure, to meet criteria for Major Depressive Disorder. Other symptoms

include significant weight gain or loss, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished ability to think, and recurrent thoughts of death. Although caregivers may not necessarily meet diagnostic criteria for a Major Depressive Episode or Major Depressive Disorder, many studies have reported on elevations in experience of depressive symptoms and their negative impact on social, occupational, or other functioning, as well as CGs' overall quality of life (Pinquart & Sörensen, 2003; Schulz & Martire, 2004; Schulz & Williamson, 1991).

Depressive symptoms have a profound influence on CGs' overall quality of life and functioning, especially as they may increase AD CGs' risk for developing physical health problems (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991; Pinquart & Sörensen, 2003) and reduce their capacity for self-care (Vitaliano, Zhang, & Scanlan, 2003). A vast literature has investigated the hypothesis that depression may increase the risk for developing CVD. An influential review paper summarizing findings from scientifically rigorous studies implicated depression as an independent risk factor for morbidity and mortality due to CVD (Musselman, Evans, & Nemeroff, 1998). According to this review, individuals with higher rates of depression display alterations in physiologic systems that increase their vulnerability for developing CVD. Examples of such changes include hyperactivity of the sympathetic nervous system, reduced heart rate variability, changes in platelet receptors, and ventricular instability. A meta-analysis conducted by van der Kooy and colleagues (2007) further identified depression as a consistent risk factor for the onset of myocardial infarctions, (i.e., heart attacks), in which damage to cardiovascular tissues occurs as a result of insufficient blood flow to parts of the heart.

In addition to elevations in depressive symptoms, AD CGs also demonstrate increased CVD risk compared with non-CGs (Aschbacher et al., 2009; Capistrant, Moon, Berkman, & Glymour, 2012; Mausbach et al., 2012; Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007; Mausbach et al., 2011). Higher CVD risk (e.g., myocardial infarction) and poorer cardiovascular prognosis have been shown to be related to elevations in biological risk markers Interleukin-6 (IL-6) (Bermudez, Rifai, Buring, Manson, & Ridker, 2002; Georges et al., 2001; Miyao et al., 1993; Ridker, Rifai, Stampfer, & Hennekens, 2000; Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000) and D-Dimer (Danesh et al., Cushman et al., 2003; 2001; Eichinger et al., 2003; Lowe et al., 2004; Pradhan et al., 2004). IL-6 is a cytokine that is secreted in response to psychological stress. It is a product of the inflammatory response, which may mediate atherosclerotic processes that increase risk for cardiovascular events (Libby, Ridker, & Maseri, 2002; Liu et al., 2006). D-Dimer is an antigen that indicates activity of the coagulation system (Danesh et al., 2001; Lowe et al., 2004). Danesh and colleagues (2011) reported that high elevations of D-Dimer indicate excessive activation of the coagulation system. Moreover, moderate increases in D-Dimer may reflect small elevations in blood coagulation, thrombin formation, and turnover of fibrin, all of which increase risk for cardiovascular events. Overall, elevations in both IL-6 and D-Dimer have been shown to be associated with heightened risk for CVD.

As CVD is the leading cause of death in women (Casper et al., 1999), and most CGs are female, female CGs comprise a vulnerable group for morbidity and mortality from CVD (Kannel, 2001). Thus, addressing depression in AD CGs may have a critical impact on public health due to its ties with both overall well-being and CVD risk

(Aromaa et al., 1994; Joynt, Whellen, & O'Connor, 2003; Musselman et al., 1998). Moreover, the estimated value for informal caregiving in dementia is over \$210 billion annually (Thies & Bleiler, 2011). Addressing CGs' depression and associated risk for CVD may extend the time that individuals can spend caregiving and delay institutionalization (Mittelman, Haley, Clay, & Roth, Cohen et al., 1993; 2006), which can reduce care-related costs to society. Thus, it behooves researchers to provide more targeted interventions to improve depression and reduce CVD risk in CGs.

Summary of Existing Caregiver Interventions

A vast array of interventions is available to help CGs cope with the stressors that they encounter on a daily basis. These include support groups, respite services, cognitive behavioral therapy (CBT), behavior modification training for addressing behavioral problems in AD patients, behavioral activation (BA), and multicomponent programs that include a variety of these services. Amidst the existing interventions for CGs, an evaluation of efficacy depends on the outcome in question. CG interventions can target the subjective experience of caregiving, including but not limited to, CG burden, quality of life, depression, anxiety, and coping ability. CG interventions have also examined the impact on CGs' physical health, as well as delaying placement of the care recipient into a long-term care setting. Overall, randomized controlled trials (RCTs) and meta-analyses suggest that these interventions are more efficacious than treatment-as-usual or control conditions for reducing depression in CGs. However, most effect sizes reported in the literature are small to medium for their impact on depression (Sörensen, Pinquart, & Duberstein, 2002). As few CG intervention studies have measured physical health outcomes, there are limited available data regarding their effect sizes for CVD risk.

Respite Care

Respite is defined as “planned, temporary relief for the primary CG through the provision of substitute care” (Gottlieb & Johnson, 2000). The aim of respite care is to help improve the physical and mental health of CGs by providing them a temporary reprieve from their ongoing caregiving duties. The respite care options available for CGs include day programs based in community centers, in which the care recipient is provided with care for a certain number of hours during the week. Another option is in-home respite, in which a health care worker with the appropriate qualifications based on the care recipient’s needs comes to the CG’s home to provide care and services to the care recipient. Lastly, institutional respite provides 24-hour care to care recipients during a short term stay. These are typically used when a CG is ill, planning a vacation, or competing demands create considerable obstacles to being able to provide care. A review by Gottlieb and Johnson (2000) evaluated the mental health impact of respite programs on CGs and found that the actual utilization of respite programs fell far below the reported demand. In general, they found mixed results for the efficacy of respite care in reducing depression, anxiety, and level of stress and burden reported by CGs. The authors argued that the inconsistent findings may be explained by study sample differences, differences in instruments used to measure outcomes, and variability in the time and intensity of respite programs. Furthermore, the authors argued that CGs may be seeking out respite care after having already exhausted themselves by caregiving for several years. A limitation of this review was the lack of quantitative comparison of effect sizes across the studies reviewed as well as the inclusion of only 6 studies. A meta-analysis by Sørensen and colleagues (2002) provided a review of 1 randomized trial testing respite

care; this study reported an effect size of Hedge's $g = .34$ for reducing CG burden and Hedge's $g = -.29$ for reducing CG depression. Using Cohen's guidelines for interpreting effect sizes, respite services appear to have a small to medium effect on reducing psychological distress, including depression, in CGs. However, the dearth of high quality randomized trials investigating the efficacy of respite care on CGs mental health limits the conclusions that can be drawn about whether or not respite care provides clinically meaningful reductions in CG depression.

Psychoeducation

Psychoeducational interventions tend to be structured in providing information about the care recipient's course of illness, what resources are available to CGs, as well as skills and services that may aid CGs in addressing dementia-related problems. A meta-analysis conducted by Thompson and colleagues (2007) reported that 5 group-based psychoeducational interventions on average demonstrated large effects (Hedge's $g = -.71$) for reducing depression in CGs compared to a control condition. The average effect size of 7 individual psychoeducational intervention trials fell in the small to medium range (Hedge's $g = -.21$) for reducing depression in CGs. However, findings from this meta-analysis are limited by the poor quality of studies that were included. Study quality was compromised by lack of blinding or insufficient information regarding blinding of participants and investigators, selective reporting of outcomes, a small number of studies included, and infrequent use of intent-to-treat analysis. Furthermore, the effects of psychoeducation may be confounded with the supportive aspect of being in a group. Sørensen and colleagues (2002) conducted a meta-analysis of 38 studies comparing psychoeducation with a control condition and reported small to medium on CG burden

effects (Hedge's $g = -.12$) and depression effects (Hedge's $g = -.23$) in randomized studies. Overall, it appears that psychoeducational interventions have small to medium effects on CG depression.

Supportive Interventions

Supportive interventions are usually carried out in a group setting, and are characterized by having a space to discuss problems that CGs encounter, share and receive information about meeting both CGs' and care recipients' needs, as well as the emotional experience of being a CG. Either a mental health provider or peer can facilitate these support groups. Sørensen and colleagues (2002) reported small average effects for 5 supportive interventions in reducing depression (Hedge's $g = -.09$), and medium effects for 4 supportive interventions in reducing CG burden (Hedge's $g = -.35$).

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT), originally developed by Beck, Rush, Shaw, and Emery (1979) to treat depression, focuses on identifying core negative schemas that impact individuals' thoughts about themselves, others, and the world. One key element of change is helping individuals to identify and challenge maladaptive patterns of thinking that increase feelings of depression, and eventually replace these with more neutral and adaptive thoughts. Another key element of CBT is BA, which involves the planning and scheduling of activities that will help alleviate feelings of depression. Therapists also help individuals develop and use problem solving skills to address the ongoing problems in their lives. Sørensen and colleagues (2002) conducted a meta-analysis on CG interventions, and found that CBT reduced CG burden with a Hedge's g effect size of -

.22 and depression with an effect size of $-.27$. These effect sizes fall within the small to medium range.

Multicomponent Programs

Multicomponent programs offer a variety of services to help CGs reduce the burden of caregiving as well as its associated psychological distress. Interventions comprising multicomponent programs may include education about caregiving, support, respite, psychotherapy, family therapies, and behavioral management (Schulz et al., 2003). The Resources for Enhancing Alzheimer's Caregiver Health (REACH) II study conducted by Gitlin and colleagues (2003) tested the efficacy of multicomponent interventions in improving CG outcomes and found that the combination of family-based multisystem in-home intervention and computer telephone integration system reduced depressive symptoms by $.23$ standard deviation units. The meta-analysis conducted by Sørensen and colleagues (2002) found that 4 randomized trials of multicomponent interventions reduced depression with an average Hedge's g effect size of $-.02$ and CG burden by $-.65$. Researchers (Schulz et al., 2003; Sørensen et al., 2002) have advocated the use of multicomponent programs to better tailor interventions toward individual needs of the CGs. However, a persistent challenge of summarizing the efficacy of multicomponent programs lies in the heterogeneity that exists within these interventions. Future research should elucidate which specific combinations of interventions provide clinically meaningful reductions in CG depression, burden, and other outcomes.

Caregiving Across Diverse Samples

Cultural variations exist with regards to attitudes about caregiving, kinship, cohabitation, social support, as well as motives for caregiving (Dilworth-Anderson et al.,

2005). Several theories have been proposed with regards to how culture influences stress and CG burden. Although classical models of CG burden have omitted cultural factors, an updated sociocultural stress and coping model of caregiving (Knight & Sayegh, 2009) proposed that cultural factors may come into play in social support and coping processes. Despite the common belief that minority CGs receive more informal support from their social networks, a meta-analysis (Dilworth-Anderson, Williams, & Gibson, 2002) found that there existed multiple layers of complexity in the informal support that individuals receive. Groups varied in their satisfaction with informal support, likelihood of reaching out to others for help, need for formal services, number of caregiving helpers. Moreover, age, gender, and relationship between the CG and care recipient can also impact a CG's satisfaction with social support received. Altogether, these authors found that perception of receiving support was most predictive of CG outcomes.

An alternative model suggests that culture may impact perceived burden and stress from being a CG (Haley et al., Farran, Miller, Kaufman, & Davis, 1997; 1996). There have been mixed findings with regards to the comparative levels of burden and depression in CGs of different racial groups (Dilworth-Anderson & Gibson, 2002). This may be explained by differences in sample size and an underrepresentation of ethnic minorities in many CG studies, measurement issues in using different scales, and sample variation as a result of different recruitment methods. Moreover, reports of higher CG burden do not consistently predict worse physical health, as illustrated by a recent meta-analysis investigating ethnic differences in CG outcomes (Martin Piquart & Sørensen, 2005). These authors highlighted the importance of viewing both the advantages and disadvantages of minority status and recognizing that they are not uniform across groups.

Beyond racial groups, further research must explore the impact of belonging to these groups as these may be more proximal determinants of CG outcomes rather than group membership alone.

Barriers to care remain a major concern in both patients with dementia as well as their CGs. A recent study found that unmet needs in CGs was positively associated with belonging to an ethnic minority group, lower socioeconomic status, and lower education levels (Black et al., 2013). Moreover, unmet needs are associated with higher levels of depression in CGs. Many services and interventions exist to meet the needs of CGs. However, the question of which interventions benefit which groups of CGs arises. A recent systematic review of the family CG intervention literature (Napoles, Chadiha, Eversley, & Moreno-John, 2010) noted that 18 of 47 intervention studies investigated outcomes by ethnic group. They also reported that only 11 integrated cultural tailoring through addressing language, literacy, familism, and barriers to care. Studies focusing on ethnic minorities included African-Americans, Latinos, and Chinese-Americans. African-Americans appeared to decrease burden, improve affect, increase happiness ratings, and increase self-efficacy for helping with IADLs from interventions involving multi-component skills training or social support. Latinos who went through skills training or psychoeducation also reported decreased burden, depression, and self-efficacy. The 1 behavioral management intervention for Chinese-Americans tailored treatment for in-home services and language preference, which resulted in decreased depression and upset from behavioral problems. The authors of this systematic review encouraged future work to focus on potential interaction effects of ethnicity and treatment on health outcomes.

Limitations of Caregiver Intervention Literature

Despite the promise of CG interventions, the average effect sizes reported in the literature remain small to medium at best for reducing depression in CGs (Schulz et al., 2002; Sörensen et al., 2002). Moreover, data are limited with respect to the effect of interventions on CVD risk, as few studies have investigated the impact of CG interventions on physical health risk among CGs. To improve the impact of CG interventions on depression, researchers have recommended tailoring of interventions based on CGs' specific needs. However, aside from reports by Schulz and colleagues (2003), the specific mechanisms responsible for reductions in depression and CVD risk after interventions are largely unknown. Thus, the CG intervention literature in general lacks a sophisticated understanding of the mechanisms (i.e., mediators) through which evidence-based treatments reduce mental and physical health problems. To improve treatment efficacy and efficiency in CGs, first we must understand the mechanisms leading to change after an intervention.

Additionally, given the heterogeneity in CGs and their caregiving situation, a more tailored intervention approach may enhance the mental and physical health benefits derived from specific interventions. Meta-analyses of intervention studies have recommended multicomponent interventions, but it is unclear which combinations of interventions are most impactful for which CGs. To date, few evidence-based treatment recommendations exist for tailoring interventions for CGs given their specific caregiving situation. Thus, we must understand the caregiving situation-related factors that may impact (i.e., moderate) psychological and biological response to interventions. Addressing these gaps in the CG intervention literature requires an investigation of the

specific moderators that change CG outcomes in depression and CVD risk post-intervention. Thus, the current study explored potential mediators and moderators of reductions in depression and CVD risk after a pleasant events behavioral activation intervention.

Why Behavioral Activation?

The BA model of depression postulates that depression stems from the occurrence of adverse life events, which leads to behavioral responses to these events (Jacobson, Martell, & Dimidjian, 2001). Avoidant behaviors, including inactivity and withdrawal, are conceptualized as behavioral patterns that provide short-term relief from adverse events. Thus, they are a common coping response to immediate distress caused by major life stressors. However, over time, continued avoidance can also deprive the individual of experiences that may enhance positive emotion or attenuate negative emotion. For example, an individual who experiences depressed mood may decide to withdraw from social situations, choosing instead to spend time alone. This person will likely also avoid social situations, including interacting with friends, coworkers, family members. Repeated withdrawal from one's social network and pleasurable activities can exacerbate the experience of depression in the long term. Although the role of genetic risk and vulnerability to emotional distress are also recognized by the BA model of depression, it is postulated that withdrawing from pleasurable activities is the mechanism through which individuals transition from being at risk for depression to experiencing persistent symptoms depression.

As the BA model postulates that individuals experience depression as a result of withdrawing from pleasurable and meaningful activities, it follows that increasing one's

engagement in such activities attenuate symptoms of depression. BA therapy focuses on increasing individual's engagement in pleasurable activities that also foster a sense of personal mastery. Personal mastery involves a sense of feeling in control over one's life, and most closely reflects one's beliefs to achieve a desired outcome (Pearlin, Nguyen, Schieman, & Milkie, 2007). Thus, engaging in pleasurable activities can boost one's mood states not only by attenuating negative emotion and enhancing positive emotion, it can also increase one's sense of confidence in the ability to effect changes in one's life. A seminal dismantling study provided a compelling argument that BA alone can achieve comparable reductions in depressive symptomatology compared to CBT and a combination of other therapies (Jacobson et al., 1996). In two recent meta-analyses reporting effect sizes of RCTs comparing BA vs. a control condition, BA interventions demonstrated a large effect for reduced depressive symptoms in adults (Cuijpers, Van Straten, & Warmerdam, 2007; Ekers, Richards, & Gilbody, 2008). Furthermore, when comparing BA alone to CBT, only small differences were found in adult depressive symptoms post-treatment. In a meta-analysis completed by Ekers and colleagues (2008), no differences in depressive symptoms were observed between BA and CBT at follow-up, with follow-up time averaging 4 months after treatment. When compared with supportive therapy and brief psychotherapy, BA demonstrated large effects in reducing depressive symptoms. CG interventions can require extensive resources, including CGs' time, therapist training for more complex interventions, availability of multiple staff members for multicomponent interventions, and the financial cost of respite care provision. Considering the savings in financial cost, human resources, and time, a focus

on BA as treatment for depression in CGs appears to be a more cost effective intervention, yet it appears to be equivalent to CBT in efficacy.

In addition to the promise of BA interventions in addressing depression in a clinical population, the BA model of depression can also be used to explain the development of depressive symptoms in CGs. For example, CGs often state that they feel limited in their freedom and ability to participate in pleasurable activities because they feel that they are constantly on caregiving duty (Schulz & Martire, 2004). The limitations in the engagement of activities that have potential to improve CGs' mood seem to exacerbate their experience of depressed affect. The experience of CGs is consistent with the activity restriction model of depressed affect (See Figure 1; Williamson & Shaffer, 2000) which postulates that individuals who are constricted in their engagement in pleasant activities will exhibit higher symptoms of depression due to reductions in positive mood and enhancements of negative mood (Mausbach, Patterson, & Grant, 2008; Williamson & Shaffer, 2000). Consequently, one would expect interventions that reduce level of activity restriction to alleviate or attenuate symptoms of depression due to its association with increased positive affect and reduced negative affect. As BA has demonstrated large effects in reducing depressive symptoms in adults, our research group conducted an RCT of a pleasant events scheduling BA intervention in CGs and evaluated its efficacy on depressive symptoms and CVD risk factors (Moore et al., 2013).

Pleasant Events Program (PEP)

The Pleasant Events Program (Moore et al., 2013) was an RCT of a BA intervention focusing on pleasant events scheduling on spousal AD CGs ages 55 and older (N= 98). CGs were randomized into either the PEP treatment condition, which had

a behavioral emphasis on engagement in pleasant activities, or a time-equivalent Informational-Support (IS) control condition, in which CGs were provided with resources and information on caregiving, as well as supportive listening. In the IS condition, there was no focus on setting behavioral goals to engage in pleasant activities. Rather, CGs randomized to the IS condition were given 4 weekly in-person sessions, followed by 2 weekly telephone sessions that involved supportive listening and providing information about caregiving. In the PEP condition, CGs were given 4 weekly in-person sessions, followed by 2 weekly telephone sessions that focused on scheduling of pleasant events and activities to improve depressive symptoms. With the help of a therapist, CGs in the PEP condition identified activities that they found enjoyable. For homework, they were encouraged to engage in these activities throughout the week. Assessors, technicians, and the research nurse were blind to CGs' treatment conditions. It was not possible to keep therapists blind to treatment condition, but attempts at blinding included keeping therapists unaware of the study hypothesis. Treatment efficacy was determined using co-primary outcomes measured both at baseline and post-treatment (i.e., 6 weeks follow-up). Co-primary outcomes included CG self-reported depressive symptoms, as well as biological CVD risk markers-Interleukin-6 (IL-6) and D-Dimer. Higher plasma levels of IL-6 and D-Dimer are respectively implicated in increased inflammatory response and coagulation of blood, both of which appear to elevate risk for CVD. The RCT found that CGs in the PEP condition achieved a significant reduction in depressive symptoms at 6-week follow-up compared to the control IS condition (Cohen's $d = .42$). CGs in the PEP condition also showed reductions in IL-6 (Cohen's $d = .52$), which suggested efficacy of the intervention for reducing CVD risk.

Investigation of Mediators

Despite the promise of BA interventions such as PEP for addressing depressive symptoms in CGs, few studies have explored mediators or mechanisms through which these interventions achieve their outcomes. Moreover, few studies have directly tested whether the reduction in depressive symptoms is a mechanism through which CVD risk can be reduced in CGs. The current study provided insights into the mechanisms (i.e., mediators) that explain why PEP reduces depression and CVD risk in spousal CGs ages 55 and older.

In accordance with the activity restriction model of depressed affect and BA model of depression, the act of partaking in pleasant activities should theoretically reduce one's negative affect and increase the probability of experiencing positive affect. This in turn should lower one's overall experience of depression. Moreover, a study by Mausbach et al. (2008) demonstrated that activity restriction significantly mediated the relationship between CG status and depression; in other words, they found that activity restriction explains why CGs are depressed compared to non-CGs. Thus, change in either pleasant activities or activity restriction may explain why CGs in PEP have reduced depression.

Personal mastery, defined as the belief that one possesses control over one's life and its obstacles, has also shown promise for protecting against negative mental health and physical health outcomes. In particular, personal mastery may attenuate the relationship between CG stress and psychiatric morbidity (Mausbach et al., 2006). Additionally, there is evidence that personal mastery may protect against health risk (Mausbach et al., 2007) and mortality (Penninx et al., 1997).

Specific Aim 1

Explored mediators that explain why PEP leads to reductions in depressive symptoms in CGs. Further, the current study explored whether or not reductions in depression mediate changes in CVD risk marker IL-6 after PEP. Depression was measured with the self-reported Center for Epidemiologic Studies-Depression Scale-10 item version (Lenore S. Radloff, 1976), and plasma levels of IL-6 served as a measure of CVD risk, with lower levels indicating lower risk for CVD.

Hypothesis 1.1: PEP leads to reductions in perceived activity restriction, increases in pleasant events, and an increase in personal mastery, which lead to improvements in depression among CGs.

Hypothesis 1.2: PEP leads to reductions in depression, which leads to reductions in IL-6 among CGs.

Investigation of Moderators

Literature Review: Moderators of Caregiver Interventions

Beyond the importance of exploring mechanisms/mediators of change, little is known regarding the specific characteristics of caregiving situations (e.g., disruptive behaviors in AD patient, use of respite services) that may moderate CGs' response to a pleasant events BA intervention. A review of the CG intervention literature suggests that characteristics of interventions, CG-specific characteristics (e.g. age, gender, relationship to care recipient), and characteristics of the caregiving situation (e.g., subjective stressors related to caregiving) can moderate the effect of various interventions on CG outcomes.

Sörensen and colleagues (2002) conducted a meta-analysis of a multitude of interventions, including support groups, CBT, psychoeducation, multicomponent

interventions, respite/day care, care recipient training, to investigate intervention-specific characteristics that may moderate intervention outcomes. They found that group interventions demonstrate smaller effects than individual interventions for improving CG burden and well-being. They also reported that longer duration of intervention may be more beneficial for improving depressive symptoms because of continued support from professionals or support groups. Higher proportions of female CGs in an intervention are affiliated with more improvements in subjective burden, but not depression.

Caregiving-situation specific characteristics that impact intervention outcomes include objective burden of caregiving, which can be measured by the amount of time CGs spend performing tasks for their care recipient or the number of years they have spent caregiving (Sörensen et al., 2002). Sörensen and colleagues (2002) also found that objective burden at baseline moderated outcomes in depression such that higher objective burden reduced the benefits of interventions in subjective burden and depression outcomes. This finding suggests that CGs who provide a higher level of care without respite may be at heightened risk for continued feelings of depression and burden. In a similar vein, Hatch, DeHart, and Norton (2014) reported that CGs who used a home health aide achieved greater reductions in depression from a multicomponent intervention than CGs who did not use a home health aide. Moreover, CGs with higher baseline depression levels exhibit greater reductions in depressive symptoms after a multicomponent intervention than CGs with lower baseline depression levels (Hatch et al., 2014). An updated meta-analysis including various interventions (Sörensen et al., 2002) corroborated these findings and reported that CGs who reported higher burden and depression at baseline exhibited greater effect sizes for these outcomes post-intervention.

CGs who experienced higher levels of stress associated with memory and problem behaviors from the care recipient demonstrated less improvement in depression after a multicomponent intervention than CGs who reporting lower stress associated with these problems (Hatch et al., 2014). However, this interaction effect became non-significant when it was tested in a model including two other interaction effects involving baseline depression levels and use of a home health aide. Lastly, a study comparing CBT psychoeducation with an enhanced support condition (Rabinowitz et al., 2006) demonstrated that CGs with low baseline self-efficacy demonstrated more improvement in depression after CBT psychoeducation than CGs in the enhanced support condition.

CG characteristics that impact treatment include the nature of the CG's relationship to the care recipient. Adult child CGs seem to derive more benefit from CG interventions than spousal CGs (Burgio et al., 2009; Sørensen et al., 2002). The authors explained that spousal CGs are more likely to have developed coping strategies from having provided care for their parents. Thus, it appears that adult children have more potential to benefit from the skills and coping strategies taught in CG interventions. The environment in which the CG lives also appears to have an impact on the efficacy of interventions on subjective burden. In particular, CGs who live in urban settings may evidence greater reductions in subjective CG burden because of greater access to resources (Burgio et al., 2009).

Despite the insights gleaned from previous studies of intervention moderators, the aggregation of data from several types of interventions may obscure potential moderator effects that are intervention-specific (Stice, Marti, Shaw, & O'Neil, 2008). Thus, the current study attempted to identify caregiving situation-related characteristics that may

moderate CGs' response to PEP, a BA intervention focused on pleasant activities.

Correlates of depression and activity restriction provide clues into potential moderators of treatment response. In other words, aspects of caregiving that may prevent CGs from being able to fully engage in PEP and complete homework assignments were targeted as moderators of treatment outcomes.

Vulnerability

In line with the Activity Restriction Model of Depressed Affect, a replicated finding is that increased dependence on CGs for completing activities of daily living (ADLs) and instrumental activities of daily living (IADLs) is associated with higher depression and CG burden (Berger et al., 2005; Covinsky et al., 2003). ADLs are defined as daily activities that are relevant to self-care (e.g., dressing, grooming and bathing), whereas IADLs are activities relevant to independent living (e.g., handling medication and finances) (Katz, 1983). Due to increased dependence of the care recipient, CGs may experience more severe limitations on their time and energy to engage in self-care behaviors (e.g., sleep, exercise, and weight maintenance) (Burton, Newsom, Schulz, Hirsch, & German, 1997; Gallant & Connell, 1997), and may be at increased risk for negative health behaviors (Beach, Schulz, Yee, & Jackson, 2000) and physical health problems (Shaw et al., 1997). Moreover, having conflicting demands on CGs' time and resources may serve as a barrier to engagement in treatments, such as PEP (Staudt, 2007). To address constraints imposed by the level of care required by a care recipient, respite services can provide CGs with a reprieve from their duties and increase the likelihood that CGs will have the time and energy to engage in PEP. Respite care can include day care programs, in-home care, and other services. Vulnerability has been conceptualized

as the ratio of number of hours caregiving vs. respite that a CG receives (Mills et al., 2004). Mills and colleagues (2004) have conceptualized CGs who provide a high level of care relative to receiving a limited amount of respite as vulnerable. In particular, they classified CGs who provided care 12+ hours per day and received respite less than once per month as vulnerable. As these studies have shown vulnerable CGs to be at higher physical and mental health risk, it is possible that vulnerability may interfere with CG's ability to engage in interventions such as PEP, which requires allotting time to engage in pleasurable activities.

Disruptive Behaviors

Disruptive behaviors in care recipients increase burden and depression in AD CGs (Schulz & Williamson, 1991; Teri, 1997). In particular, a cross-sectional study found that increased care recipient mood and disruptive behaviors (e.g., anger, aggression) placed CGs at higher risk for meeting criteria for depression (Covinsky et al., 2003). Care recipient disruptive behaviors are affiliated with higher activity restriction (Bookwala & Schulz, 2000) in CGs, as well as poorer CG health (Pinquart & Sörensen, 2007). Moreover, behavioral interventions focusing on problem solving for care recipients' problem behaviors show promise for alleviating depressive symptoms (Teri, Logsdon, Uomoto, & McCurry, 1997). Thus, the presence of care recipient disruptive behaviors may counteract PEP's goals of alleviating depression and CVD risk in CGs.

Social Support

Social support can take many different forms, including emotional support, informational support, and instrumental support. The positive relationship between social

support and better mental health outcomes is well established (Almedom, 2005; Uchino, 2006). Moreover, many studies have replicated this relationship in Alzheimer's CGs (Pinquart & Sörensen, 2007; Schulz et al., 1995; Wilks & Croom, 2008). In fact, a study testing an intervention targeting social support in Alzheimer's CGs demonstrated that increased satisfaction with one's social support system can mediate the impact of the intervention on CG depression (Roth, Mittelman, Clay, Madan, & Haley, 2005). As PEP targets pleasurable activities, having social support may impact the feasibility that a CG will be able to engage in these activities. Moreover, as pleasurable activities often include tasks that involve individuals in one's social network, e.g., going to lunch with a friend, having a limited social support system can reduce the frequency or enjoyment of pleasurable activities. Thus, social support was tested as a moderator of the relationship between PEP and depression outcomes in CGs.

Working Status

Work stress and high demand from work have strong ties to depression. A study exploring this relationship found that individuals who experience chronic work-related stress are 1.8 times more likely to meet criteria for a depressive disorder than individuals who do not experience chronic work-related stress (Siegrist, 2008). Although the current study did not specifically measure CG's perception of work-related demands and stress, data about hours worked per week were collected, which reflect time demands of work. There is evidence that higher workload related to CG duties is associated with higher depression (Juratovac, 2009). CGs who are concurrently employed may encounter greater difficulty with adhering to recommendations to engage in pleasurable activities. Thus, the

current study investigated the potential impact of professional workload on CG's mental health outcomes after PEP.

Baseline Depression

To replicate findings from previous studies, the current study investigated baseline depression as a moderator of outcomes after PEP. Previous studies have reported that CGs who have lower baseline levels of depression will demonstrate less improvement in their depressive symptoms post-treatment (Hatch et al., 2014; Sørensen et al., 2002).

Specific Aim 2

In summary, the second major aim of the current study was to identify variables that moderate response to PEP among CGs. Proposed moderators include CGs' baseline depression, use of respite services, number of hours the CG is currently working, CG report on care recipient's disruptive behaviors, and CG vulnerability based on ratio of respite obtained vs. hours spent in caregiving duties.

Hypothesis: Not using any respite services, higher reports of disruptive behaviors, and higher CG vulnerability will attenuate benefits derived from PEP due to their impact on CGs' ability to engage in treatment and prescribed activities from treatment.

Moreover, CGs who have lower levels of depression at baseline were expected to benefit less from PEP than CGs who report high baseline levels of depression. It was expected that CGs who do not utilize respite services to help meet their care recipients' needs will have less time to focus on engaging in pleasant activities required by PEP. Thus, they may feel more restricted in their abilities to partake in pleasant activities, and the competing priorities of having to complete more tasks for their care recipient may restrict

the time and energy they have to engage in the intervention. Similarly, CGs whose care recipients display higher levels of disruptive behaviors may be preoccupied with managing their care recipient, which can limit their ability to engage in treatment. Moreover, the BA model of depression argues that depression arises from adverse life events and responses to these events. It is possible that the positive affect that results from engaging in PEP may not be sufficient to counter-balance the negative affect experienced by CGs as a result of disruptive behaviors from their care recipients.

Exploratory Analyses: Differences between responders and non-responders

Differences between responders (i.e, those who achieve a 50% reduction in depression, IL-6, and D-Dimer) vs. non-responders (i.e, those who achieve <50% reduction in depression, IL-6, and D-Dimer) to treatment were investigated. Variables of interest included CGs' recipient's disruptive behaviors, social support, working status, personal mastery, self-rated overall health, years caregiving, number of hours of caregiving per day, and number of hours on duty.

Summary of Aims

The current study's objective was to conduct a secondary analysis of a completed Pleasant Events Program (PEP) intervention study CGs ages 55 years or older (Moore et al., 2013), which tested the efficacy of a pleasant events behavioral intervention versus a time-equivalent information-support control condition. Both treatment and control groups completed 4 weekly in-person sessions followed by 2 weekly telephone sessions. Primary and secondary outcomes were measured at baseline and at 6-week follow-up. The primary outcome was CGs' self-reported depression, and secondary outcomes were plasma levels of CVD risk markers Interleukin-6 (IL-6) and D-Dimer. Elevations in IL-6

indicate heightened inflammatory processes (Akira, Hirano, Taga, & Kishimoto, 1990; Ferrucci et al., 1999) and elevations in D-Dimer indicate higher activity in the coagulation system (John Danesh et al., 2001; Lowe et al., 2004), both of which heighten risk for CVD.

Aim 1: Mediators

The current study uncovered mediators, or mechanisms, through which PEP leads to reductions in depressive symptoms and CVD risk markers in CGs; it also explored the individual and interpersonal factors that may moderate CGs' responses to PEP. Proposed mediators of depression include CGs' perceived activity restriction, self-reported engagement in pleasant events, and personal mastery. CG self-reported depression was hypothesized to be a mediator of PEP and CVD risk marker IL-6.

Aim 2: Moderators

The current study also aimed to investigate aspects of caregiver situation-specific variables that may impact treatment response to PEP. Proposed moderators included the following caregiving situation-specific characteristics: CGs' reports of the care recipient's disruptive behaviors, social support, working status, vulnerability (determined by use of respite services and hours caregiving), and baseline depression.

Aim 3: Differences between responders and non-responders

Differences between responders (i.e, those who achieve a 50% reduction in depression, IL-6, and D-Dimer) vs. non-responders (i.e, those who achieve <50% reduction in depression, IL-6, and D-Dimer) to treatment were investigated. Differences in CGs' recipient's disruptive behaviors, social support, working status, personal mastery,

self-rated overall health, years caregiving, number of hours of caregiving per day, and number of hours on duty were tested.

Relevance

The current study employed a focus on mediators and moderators of treatment efficacy through a secondary data analysis, which will expand the knowledge of why and for which CGs a pleasant events behavioral intervention in CGs reduces depression and CVD risk. The current study's aims show promise for tailoring behavioral interventions based on individual caregiving situations. Knowledge derived from this investigation has the potential to improve efficiency of pleasant events behavioral interventions aimed at reducing depressive symptoms and CVD risk in AD CGs. Uncovering the mediators and moderators of reduced depression after PEP provides an exciting opportunity to enhance quality of life in CGs and reduce costs affiliated with depression and CVD risk.

CHAPTER 2: RESEARCH METHOD

The current study was a secondary data analysis that examined variables that mediate and moderate the efficacy of PEP on primary (depression) and secondary outcomes (CVD risk markers D-Dimer and IL-6, with higher values indicating higher CVD risk) in spousal AD CGs ages 55 and older. As a part of the RCT for PEP, CGs were randomized to either the PEP condition or an information-support (IS) control condition. The current investigation tested perceived activity restriction, engagement in pleasant activities, and personal mastery as mediators of PEP treatment efficacy. The current study also tested care recipient disruptive behaviors, CG vulnerability, social support, baseline depression, and working status, as moderators of PEP treatment efficacy. Lastly, differences in caregiver situation-specific variables between responders vs. non-responders to PEP were investigated. PEP (Moore et al., 2013) was an RCT of a behavioral intervention focusing on pleasant events scheduling on spousal AD CGs ages 55 and older (N= 100). CGs were randomized into either the PEP treatment condition which had a behavioral emphasis in engagement in pleasant activities, or a time-equivalent IS control condition. In the PEP condition, CGs were given 4 weekly in-person sessions, followed by 2 weekly telephone sessions that focused on scheduling of pleasant events and activities to improve depressive symptoms. In the IS condition, CGs were given 4 weekly in-person sessions, followed by 2 weekly telephone sessions that involved supportive listening and providing information about caregiving. There was no focus on setting behavioral goals to engage in pleasant activities in the IS condition. Treatment efficacy was determined primarily based on reductions in depressive

symptoms, and secondly, based on changes in CVD markers-Interleukin-6 (IL-6) and D-Dimer. The RCT found that CGs in the PEP condition had significant reductions in depressive symptoms ($d = .42$) and on CVD risk at 6-week follow-up as demonstrated by significant reduction in IL-6 ($d = .52$).

Participants

The current sample consisted of 98 CGs who were recruited through referrals from the UCSD's Alzheimer's Caregiver study, the UCSD Alzheimer's Disease Research Center (ADRC), community support groups, health fairs, and local senior centers. Under a HIPAA waiver, telephone screening was conducted with potential participants prior to enrollment in the study to assess for inclusion and exclusion criteria. All participants were required to be currently providing in-home care to a spouse with an AD diagnosis made by a physician and be at least 55 years of age at the time of enrollment. CGs were excluded if they were taking psychotropic medications, had been diagnosed with a terminal illness with a life expectancy of less than 6 months, were cognitively impaired, were currently enrolled in an intervention study to reduce CG distress, or have a blood pressure of greater than 200/120 mm Hg. Because the current study sought to assess CGs' risk for impairing diseases, having severe health conditions excluded CGs from the study. Moreover, concurrent enrollment in an intervention study and the consumption of psychotropic medications constituted exclusion criteria, as they may confound the results for a psychological outcome such as depression.

Procedure

Moderator and mediator analyses were conducted on the efficacy of PEP treatment outcomes using data from the completed PEP intervention study. Participants

were randomized to either PEP or the IS control condition through a computer-generated algorithm. A single master's-level research staff member provided therapy sessions to all participants. If participants were lost to follow-up or discontinued treatment, their available data were included in an intent-to-treat analysis to prevent biased statistical analyses and conclusions drawn from an RCT (Lachin, 2000; Little & Yau, 1996; Mazumdar, Liu, Houck, & Iii, 1999). Data were independently entered twice by two research staff members. Any discrepancies in data entry were resolved by referencing original paper files. Multiple regression models predicting pre-post change in depression and CVD risk markers will be used in the current study to test for both mediation and moderation. These analyses will be further described in the Data Analysis section

Measurement

Primary (depression) and secondary (IL-6 and D-Dimer) outcome measures were collected at baseline, then at 6 weeks follow-up (see Table 1). At baseline, a trained research staff member went to the CGs' homes to obtain informed consent and administer the psychosocial measures described below (depression, care recipient disruptive behaviors, respite care use, respite obtained, pleasant events, and activity restriction). A registered nurse who was blind to CGs' treatment condition visited the CG at home to collect blood samples for biological assays, including CVD biomarkers D-Dimer and IL-6. All psychosocial measures and blood samples were also collected at the 6-weeks follow-up time point.

Demographic, Clinical, and Caregiving Information

At baseline, demographic information regarding age, gender, and race/ethnicity was collected from CGs. Moreover, basic information about duration of caregiving and number of hours working per week was collected.

Center for epidemiologic studies depression scale. CGs completed the short form of the Center for Epidemiologic Studies Depression Scale (Radloff, 1977) (CES-D), a 10-item self-report measure (See Appendix A) that has been shown to validly and reliably capture symptoms of depression in a non-clinical population. Items asked CGs to report the frequency with which they endorsed symptoms consistent with depression, with responses ranging from 0 = “rarely or none of the time” to 3 = “all of the time.” Items included 1) “I was bothered by things that usually don’t bother me” 2) I had trouble keeping my mind on what I was doing” 3) “I felt depressed” 4) “I felt that everything I did was an effort” 5) “I felt hopeful about the future” 6) “I felt fearful” 7) “My sleep was restless” 8) “I was happy” 9) “I felt lonely” 10) “I could not get going.” Items 5 and 8 were reverse coded, and the other items were coded as described. Scores from the 10 items ($\alpha = .53$) were then summed to create a total score, with higher total scores indicating higher depression.

D-dimer. Assays of D-dimer were determined by use of a commercially available ELISA kit (Diagnostica Stago). Each sample was measured in duplicate. If the two values differed by more than 15%, the samples were rerun. Rest and post-speaking stress reactivity measures from the same subject were measured on the same ELISA plate. For D-dimer, the precision and sensitivity performance values of this assay were excellent: intra-assay CV (%) < 5.4, inter-assay CV (%) = 4.8, and the assay sensitivity is 5ng/mL.

The laboratory technician was blind to any subject identifiers. Higher scores are indicative of higher activation of the coagulation system, and thus, higher CVD risk.

Interleukin-6. Assays of Interleukin-6 (IL-6) were determined by use of a commercially available ELISA kit (R&D Systems products). Each sample was measured in duplicate. If the two values differed by more than 15%, the sample was rerun. Rest and post-speaking stress reactivity measures from the same subject were measured on the same ELISA plate. The precision and sensitivity performance values of these assays were excellent: For IL-6, the intra-assay CV (%) is 2.2, the inter-assay CV (%) was 3.9, and the assay sensitivity was <0.11 pg/ml. The laboratory technician was blind to any subject identifiers. Higher scores indicate higher inflammatory processes, which facilitate processes that elevate CVD risk.

Revised memory and behavior problems checklist. CGs completed the Revised Memory and Behavior Problems Checklist (Johnson, Wackerbarth, & Schmitt, 2001), which asks CGs to rate the frequency of behavioral and memory problems in dementia patients using a Likert scale (0 = “never” to 4 = “occurs daily or more often”), as well as the level to which these behaviors bothered the CG (0 = “not at all” to 4 = “extremely”). The measure has 3 subscales: memory problems, affective distress, and disruptive behaviors. The disruptive behaviors subscale is comprised of 8 items ($\alpha = .67$), which included 1) “Destroying property,” 2) “Doing things that embarrass you” 3) “Waking you or other family members up at night” 4) “Talking loudly and rapidly” 5) “Engaging in behavior that is potentially dangerous to self or others” 6) “Threats to hurt others” 7) “Aggressive to others verbally” 8) “Arguing, irritability, and/or complaining.” Scores are

summed for the subscale. Higher total scores on the disruptive behaviors subscale indicate more severe disruptive behaviors.

Vulnerability. Vulnerability was determined based on previous CG studies (Mausbach, Mills, et al., 2007) in which CGs were considered vulnerable if they provided 12 or more hours of care per day and used respite services less than 1 time in the past month. CGs were asked to report the total number of hours per day in which they are doing caregiving-related activities. To measure use of respite care, CGs were presented a list of services that provided respite from caregiver and home duties and were asked whether or not they had used the following services in the past month: homemaker, home health aide, visiting nurse, or senior day care. Responses ranged from 0 = “never” to 4 = “4 or more times.” CGs were also asked to report the number of hours they spent providing actual care to their spouses. CGs were then classified as vulnerable or not vulnerable. Vulnerable CGs were those who provided at least 12 hours of care per day and had not used any respite services in the past month. All other CGs were considered as non-vulnerable, including CGs who provided over 12 hours of care per day and had used respite services.

Pleasant events schedule-AD: Short Form. The Pleasant Events Schedule-AD: Short Form (Logsdon & Teri, 1997) is a self-report measure originally intended to assess engagement in pleasant activities in older patients with Alzheimer’s Disease. In the current study, CGs were asked to report the frequency with which they engaged in 20 pleasurable activities ($\alpha = .78$) in the past month, such as shopping, having meals with friends, exercising, and going on outings, to name a few. Responses ranged from 0 = “Not at all” to 2 = “Often (7 or more times)”. The scale then asks CGs to rate the extent

to which they enjoyed each activity from 0 = “Not at all” to 2 = “A great deal”. Scores from each item were summed for a total frequency score and a total enjoyment score. Higher scores indicate higher frequency and enjoyment of activities. A previous validation study (Logsdon & Teri, 1997) demonstrated that items on this measure demonstrate high internal consistency. Moreover, significant differences in enjoyment of activities, but not in frequency of activities, were found between depressed and non-depressed older adults.

Activity restriction scale. The Activity Restriction Scale (Williamson & Schulz, 1992) is a self-report measure that asks CGs to rate the extent to which they feel restricted from engaging in 9 non-caregiving areas of activity, such as caring for themselves, visiting friends, and going to work ($\alpha = .78$). Responses ranged from 0 = “Never or seldom did this” to 4 = “Greatly Restricted”. Higher scores reflect higher activity restriction in CGs.

Personal mastery scale. The Personal Mastery Scale is a self-report measure consisting of 7 items that asks CGs to rate the extent to which they feel little/no control over what happens in their lives ($\alpha = .55$). Items ranged from 0 = “Strongly Disagree” to 3 = “Strongly Agree.” With 2 items, higher scores indicated higher sense of personal mastery (e.g. “I can do just about anything I really set my mind to.”) “ Four items were reverse scored (e.g., “There is really nothing I can do to change things in my life”). Scores were summed for a total score, with a higher value on the total score reflecting feeling less control over one’s life.

Perceived adequacy of expressive support from friends and family. An eight-item scale developed by Pearlin (McCubbin, 1998), in which CGs rate 1 = Strongly Disagree to 4 = Strongly Agree to questions assessing support received from friends and family.

For example, CGs are asked to rate the extent to which they agree or disagree with the following statement: “You have at least one friend or relative you really confide in.” One item was reverse-scored: “There is really no one who understands what you are going through.” Scores from the 8 items ($\alpha = .76$) were summed for a total score, with higher scores on this measure reflecting a higher level of perceived support from one’s social network.

Data Analysis

Data Analysis Specific Aim 1: Mediation

Mediation was used to test mechanistic pathways (MacKinnon, 2007; MacKinnon, Fairchild, & Fritz, 2007), such as the ones shown in Figures 2a & 2b. In the current study, mediation was carried out in SPSS (Nie, Bent, & Hull, 1975) using multiple regression models (Krull & MacKinnon, 2001) to calculate regression coefficients of the predictive relationships shown in Figures 3a & 3b. Once these regression coefficients for the paths were obtained, they were entered into an interactive online tool that uses the Monte Carlo method for Assessing Mediation to produce confidence interval estimates (MacKinnon, Lockwood, & Williams, 2004).

Three mediators were tested independently: activity restriction, pleasant events, and personal mastery. The first mediation model tested the pathway that PEP leads to reductions in activity restriction and increases in pleasant events, which lead to reductions in depressive symptoms. Thus, in the models, treatment condition was the independent variable and post-treatment change in depression was the dependent variable. Mediators for these mediation models were post-treatment changes in pleasant

events, activity restriction, and personal mastery. Covariates included in mediation models were CG age, sex, baseline depression, and antidepressant medication status.

Further, this study tested whether changes in depression mediate the relationship between treatment condition and cardiovascular risk outcome IL-6. Covariates included in these models include CG age, sex, baseline IL-6, body mass index, and exercise.

A limitation of using regression with longitudinal data is the deletion of cases with missing data. To prevent the loss of power, sample bias, and inflation of Type I error, it is recommended that studies utilize an intent-to-treat analytic approach to include both completers and non-completers (Lachin, 2000). Multiple imputation methods, using observed variables to make iterative predictions of the missing variable, were used to address limitations of missing data (Van Buuren, Boshuizen, & Knook, 1999). Multiple imputation is recommended above simpler methods such as carrying forward the last observation, due to problems with bias and inaccurate standard errors (Donders, van der Heijden, Stijnen, & Moons, 2006). The decision to impute dependent variables remains a topic of debate. A recent study demonstrated that analyses excluding and including imputed dependent variables yielded comparable findings in terms of both confidence intervals and statistical significance (Young & Johnson, 2010). The current study thus included both imputed independent and dependent variables for analyses.

Imputation models followed recommendations from previous studies (Sinharay, Stern, & Russell, 2001), which utilize statistical models of interest to impute missing data, including all predictor and outcome variables. Two multiple imputation models were run: one for mediation analyses and one for moderator analyses. Multiple imputation models for interaction analyses included the following variables: . 1)

Dependent Variable = pre-post change in CES-D and IL-6 2) Independent Variables = treatment condition (i.e., PEP vs. IS), baseline scores of the proposed moderators (i.e., social support, working status, baseline depression, disruptive behaviors, and vulnerability) 3) the interaction terms, which were the mathematical product of treatment condition dummy code (0 = IS; 1 = PEP) x moderator and 4) baseline value of dependent variable and 5) covariates: age, gender, depression medication status. Multiple imputation models for mediation analyses included the following variables: Dependent Variable = pre-post change in CES-D and IL-6 2) Independent Variables = treatment condition (i.e., PEP vs. IS), baseline scores of mediators (i.e., pleasant events change, activity restriction change, and personal mastery change) 3) baseline value of mediators and 4) covariates: age, gender, depression medication status.

SPSS software automatically generated these datasets, and allowed for analyses that use the mean value from these imputations. However, with a higher proportion of missing values, there exist concerns that multiple imputation will lead to biased estimates, and consequently, inaccurate conclusions (Sterne et al., 2009). Percentages of missing data are presented in Table 3. Percentages of missing data did not meet the threshold for invalid imputed estimates.

After regression coefficients and standard errors for paths a, b, and c' in Figures 3a and 3b were calculated, the Monte Carlo Method for Assessing Mediation (MCMAM) (Preacher, Zyphur, & Zhang, 2010) using an online interactive tool (Selig & Preacher, 2008) tested the three mediation models. The MCMAM uses re-sampling methods to create sampling distributions. 95% confidence intervals were generated to estimate mediation coefficients (Preacher & Selig, 2012). The current data analysis adhered to

current recommendations for directly quantifying and estimating the value of indirect effects, rather than inferring them, as suggested by the Baron and Kenny method (Hayes, 2009). Moreover, many studies have advocated for the statistical benefits of re-sampling due underpowered and biased mediation analyses (MacKinnon et al., 2007).

Data Analysis Specific Aim 2: Moderation

Moderation of the relationship between PEP intervention and depression was also conducted using multiple regression. The following hypothesis was tested for Specific Aim 2: Care recipient's disruptive behaviors, CGs' vulnerability, continued working status, lack of social support, and lower levels of baseline CG depression may attenuate depression and CVD risk benefits derived from PEP (see Figure 3). Independent sample t-tests examined baseline differences in moderators between PEP and IS treatment conditions. Three multiple regression models were tested to examine the moderators of the relationship between PEP and depression. They included the following variables: 1) Dependent Variable = pre-post change in CES-D or IL-6 2) Independent Variables = treatment condition (i.e., PEP vs. IS), baseline scores of the proposed moderators (i.e., social support, working status, baseline depression, disruptive behaviors, and vulnerability) 3) the interaction terms, which was the mathematical product of treatment condition dummy code (0 = IS; 1 = PEP) x moderator and 4) baseline value of dependent variable. The following covariates were also included in analyses: age, gender, and depression medication status. Follow-up analyses were conducted to understand the directionality of significant interactions.

Data Analysis Specific Aim 3: Differences between Responders and Non-responders

In the original PEP outcomes study, no significant differences were found in D-Dimer levels across treatment condition. Thus, exploratory analyses were conducted to examine the subgroup of individuals who responded to PEP, as defined by a 50% reduction in D-Dimer levels. In particular, independent sample t-tests investigated group differences between responders vs. non-responders in various domains that capture caregiver situation-specific variables, e.g., personal mastery and social support. This study also investigated psychosocial differences between responders and non-responders to PEP in terms of IL-6 and depression, with responders operationalized as CGs who achieved a 50% reduction in IL-6 and CES-D scores and non-responders <50% reduction.

Power Analyses

Mediation analyses. Two power analyses were conducted based on empirical estimates of sample sizes needed to achieve .8 power for the resampling methods of testing mediation (Fritz & MacKinnon, 2007). Three separate mediation models (see Figure 2a) tested if change in activity restriction, pleasant events, and personal mastery mediated changes in depression after PEP. Based on effect sizes reported in the literature, a sample of approximately 148 participants was required to achieve .8 power. As the current secondary data analysis was based on a sample of 98 CGs, this analysis may have been underpowered.

The second power analysis was conducted for the second set of mediation models (see Figure 2b, which tests change in CES-D scores as a mediator of the relationship between PEP treatment and reduction in CVD risk marker IL-6. Approximately 71

participants are required to achieve .8 power for these mediation models. Thus, the current study appeared to have sufficient power to detect these mechanistic pathways.

Moderation analyses. G*Power 3.1.9.2, a statistical power analysis program (Faul, Erdfelder, Lang, & Buchner, 2007), was used to calculate estimated power achieved by the current moderator analyses. Estimated power for moderation analyses fell between .44 and .94 (baseline depression, power = .64; use of respite services, power = .90; disruptive behaviors, power = .44). The reported power estimates were based on effect sizes reported from the literature, with depressive symptoms or CG burden as an outcome variable. However, given the limited number of intervention studies reporting statistics necessary to calculate effect sizes of moderation, the power estimates reported here may be under- or over-estimating the current study's true level of power.

Design Considerations/Potential Problems

An alternate way to conceptualize the current secondary analysis is a moderated mediation (Muller, Judd, & Yzerbyt, 2005; Preacher, Rucker, & Hayes, 2007). It may be that the mediational pathways may be different for CGs depending on their individual caregiving-specific situations. For example, perhaps PEP helps to reduce CG depression and CVD risk by reducing activity restriction, but this may only be true for CGs with enough time to engage in pleasant events due to their use of respite services. However, we chose a more parsimonious approach as mediator and moderator analyses of pleasant events interventions in CGs are limited. Future work should address more complex models of moderation and mediation in CG interventions.

Despite the current use of mediation testing for causation (Albert, 2008; Rubin, 2004), it is difficult to establish temporal primacy in the proposed mediation model, e.g.,

did PEP change activity restriction, and then change in activity restriction subsequently reduced depression in CGs? Or did PEP alleviate depressive symptoms, which then led to reduced activity restriction? Our current methods for measuring these constructs do not allow us to establish temporal order of change. In reality, these constructs may all be changing at the same time. Future studies are advised to use more sophisticated methods (e.g., ecological momentary assessment) during engagement of pleasant events, to establish the temporal order of changes in proposed mediation pathways.

CHAPTER 3: RESULTS

Missing Values

Descriptive analyses were run to explore differences in baseline scores of potential moderators between PEP vs IS treatment conditions. Descriptive statistics are displayed in tables 2 and 3. Little's Missing Completely at Random Test was non-significant ($\chi^2 = 21.7$, $df = 25$, $p = .7$) suggesting that the pattern of missingness of baseline variables were at random. Multiple imputation methods were used to fill in missing data values for both predictors and outcome variables in the statistical model.

Skewness and Outliers

Two outliers for IL-6 change variable were detected, as defined by Cook's $D \geq 4/n$ criteria (Cook & Weisberg, 1982; Jones & Juggins, 1995). These individuals were excluded from the current study, leaving a total sample size of $n = 98$. No other outliers were identified. Skew and kurtosis were addressed using the ladder of powers approach (Judd, McClelland, & Ryan, 2011). Moreover, the outcome variable of post-treatment change in IL-6 demonstrated a positive skew, which was addressed using a natural log transformation. Natural log transformation of IL-6 resulted in a normal distribution. The current study measured the number of hours that CGs were working at baseline. As many CGs included in the current study were older and retired, there was a significant skew of the data which transformations did not adequately address. Thus, this variable was treated as a categorical variable, i.e., working vs. not working, to circumvent problems with conducting analyses using variables that violate normality.

Mediator Analyses

Three mediation models were run to investigate explanatory mechanisms for why PEP led to reductions in CES-D scores in CGs post-treatment. The following mediators were investigated separately: activity restriction change, frequency of pleasant events change, and personal mastery change (See Figures 4-7). Baseline CES-D, gender, age, and antidepressant medication status were covariates for these models. Contrary to hypotheses, change in activity restriction (95% CI [-2.95, 1.96]), pleasant events (95% CI [-.27, .85]), and personal mastery (95% CI [-.50, .36]), did not significantly mediate the relationship between treatment condition and reduction in CES-D scores. Baseline CES-D significantly predicted CES-D change at $p < .05$ in all three models, while gender, age, and antidepressant medication status did not.

Further mediation analyses were run to test whether or not changes in CES-D explained the differences in biomarker IL-6 reductions post-treatment. Baseline IL-6, age, and gender were tested as covariates in this model. Results showed that changes in CES-D scores did not significantly mediate this relationship (95% CI [-.01, .01]). Baseline IL-6 was a significant predictor of change in IL-6 post-treatment (See Figure 7).

Moderator Analyses

The following variables were tested as moderators of treatment condition effects on CES-D change post-treatment: vulnerability, disruptive behaviors, baseline depression, social support, and working status. Interaction effects with treatment condition were non-significant for the following variables: disruptive behaviors ($t(97) = -.19$, $\beta = -.03$, $p = .85$), social support ($t(97) = .04$, $\beta = .01$, $p = .97$), working status ($t(97) = -.33$, $\beta = -.86$, $p = .75$), vulnerability ($t(97) = -1.52$, $\beta = -.698$, $p = .13$), and baseline

depression ($t(97) = -1.30$, $\beta = -.29$, $p = .19$). In the 5 regression models testing interaction effects, baseline depression had a significant main effect on change in depression levels post-treatment such that CGs who had higher CES-D scores at baseline achieved greater reductions in CES-D scores post-treatment, regardless of treatment condition. An independent sample t-test showed that CGs in PEP did not have higher baseline CES-D scores than CGs assigned to the IS condition: ($t(96) = -1.42$, $p = .16$). Results from the above reported regression analyses are displayed in Table 4.

Exploratory Analyses: Characteristics of Responders to Treatment

Exploratory analyses tested differences between CGs who were considered responders to PEP vs. CGs who did not respond to treatment. Response to treatment was defined as achieving a 50% or greater reduction in CES-D, IL-6, or D-Dimer. Tables 5a-5c display the number of responders and non-responders by treatment outcome and treatment condition. These analyses revealed no significant differences in caregiver situations-specific variables between CGs who achieved a 50% reduction in D-Dimer scores and CGs who did not. However, it is notable that differences in total number of hours providing care per day ($t(45) = 1.72$, $p = .09$) and overall health ($t(45) = -1.80$, $p = .08$) trended toward significance. The trend revealed that responders to treatment tended to have better self-reported overall health and provided fewer hours of care per day. CGs who achieved a 50% reduction in CES-D scores were providing care for a spouse who was significantly younger ($t(43) = 2.50$, $p = .02$). Moreover, there were non-significant trends such that CGs with 50% reduction in CES-D scores after PEP were younger than CGs who did not achieve 50% reduction: ($t(46) = 1.75$, $p = .09$). Individuals who had a

50% reduction in IL-6 scores after PEP had significantly higher baseline personal mastery ($t(30) = -3.24 p < .01$).

CHAPTER 4: DISCUSSION

Mediators

A primary aim of the current study was to explore explanatory mechanisms of change after PEP. Tests of mediation and explanatory pathways of why PEP reduces depression in CGs found no significant mediation by change in pleasant events, change in activity restriction, or change in personal mastery. Treatment condition was not a significant predictor of change in any of the hypothesized mediators. Limitations in measurement may be partially responsible for reduced power in this study. In particular, the Pleasant Events Scale lists very specific activities that CGs may engage in, e.g., dressing up, making or eating snacks, shopping, listening to music, going to lunch with friends. As the PEP intervention did not specifically target these behaviors that were listed on the Pleasant Events Scale, a shift in the Pleasant Events Scale may not necessarily occur after PEP. It is likely that CGs instead choose to engage in other pleasurable activities, which are not captured by this measure. Future studies would benefit from a more inclusive and thorough assessment of the types of pleasurable activities that CGs choose to engage in. A recent study by Hershenberg, Paulson, Gros, and Acierno (2015) utilized weekly planners and asked participants to record activities each day, classifying these activities as pleasurable, functional, or social in nature. The total number of activities was generated from this weekly planner and used for analyses. Moreover, many studies have utilized the Behavioral Activation for Depression Scale (Kanter, Mulick, Busch, Berlin, & Martell, 2007) to capture a broader range of activities that older adults may choose to execute as well as impairments in completing social and

work-related activities. Moreover, the current sample demonstrated very small changes in the Activity Restriction Scale and Personal Mastery Scale. A review conducted by Berry and West (1993) concluded that self-efficacy is expected to change over the life course; however, self-efficacy changes in late adulthood may be more subtle as they may rely more on comparisons within the self rather than with others (Bandura, 1981). Thus, these measures may be capturing constructs that remain stable over time in older adults, and may not be sensitive to changes that may occur as a result of an intervention.

It is also possible that another variable other than the proposed mediators in the current study may be explaining the reduction in depression after PEP. For instance, previous studies have demonstrated the importance of appraisal of caregiving-related stressors on CG mental health outcomes (Mittelman, Roth, Haley, & Zarit, 2004). Research on coping and acceptance suggests that although CGs may not be able to make significant changes in the circumstances of their lives, it is possible that PEP may have taught CGs to better appreciate what little time they do have to pursue pleasurable activities. Namely, positive reappraisal or learning to accept one's situation may play a role in CG's reduced depression after a behavioral activation intervention (Brannen & Petite, 2008). Moreover, although CGs did not reduce their perceptions of activity restriction, they may better appreciate the small instances in which they are not restricted in pleasurable activities. Contrary to hypotheses and the activity restriction model of depression, a reduction in AR does not account for reductions in depression after PEP. Perhaps reductions in depression are achieved through altered perceptions of CG's

situations, specifically in their affect or level of enjoyment of the activities that they are actually able to engage in.

Baseline levels of personal mastery independently predicted change in depression scores after treatment, even when controlling for the effect of baseline depression, suggesting that personal mastery may be better conceptualized as a moderator of treatment effects, rather than a mediator. A study conducted by Rabinowitz et al. (2006) tested self-efficacy as a moderator of differential treatment outcomes and found that low self-efficacy predicted better treatment response in a cognitive behavioral psychoeducational intervention. Thus, CGs who have lower levels of baseline personal mastery may be expected to experience greater benefits from PEP, and can be expected to have a greater reduction in depression from PEP than CGs who had a higher level of baseline personal mastery.

Moreover, analyses testing depression change as a mediator of the relationship between treatment condition and changes in IL-6 was non-significant. Previous studies have tested inflammatory markers as mediators of depression outcomes. Studies utilizing animal models show mixed results in trying to find a causal relationship of cytokines on depression. Moreover, multiple systems are involved in depression and chronic stress, such as the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system, and corticotrophin releasing hormone. Previous studies have shown that corticotrophin releasing hormone (Friedman & Irwin, 2001; Strausbaugh & Irwin, 1992), sympathetic neurotransmitters (Sanders & Straub, 2002), and the HPA axis (Macs et al., 1996) may mediate the relationship between immune function and depression. Future studies would benefit from inclusion of a wider range of the biological mediators of depression and

inflammation. Furthermore, immune function and inflammatory markers are impacted by BMI, physical activity, smoking, alcohol consumption, sleep and other lifestyles factors (e.g., socioeconomic status) (Irwin & Miller, 2007). Although older spousal CGs may experience reductions in depression after PEP, this change does not necessarily translate to improved self-care and health behaviors, which also have a strong impact on inflammatory processes. Future interventions studies incorporating health behavior change may capture greater change in physical health markers.

Moderators

Overall this study did not find any significant moderator effects of vulnerability, disruptive behaviors, baseline depression, social support or working status on treatment response in CGs who underwent PEP vs. IS. One possible explanation for this is the fact that true interactions are already difficult to detect in practice. Moreover, PEP as a study was not specifically designed to maximize power of detecting interaction effects. A limited range in the values of moderators may have reduced power to detect interaction effects (Frazier, Tix, & Barron, 2004). In particular, most CGs were classified as non-vulnerable. Future studies will need a larger and more diverse sample, utilizing oversampling methods, to capture a higher level of variability in vulnerability, work status, and other potential moderators of PEP treatment response.

Beyond moderator effects, this study found that baseline depression had a significant main effect on change in depression scores post-treatment. This finding shows that CGs who reported higher depression at baseline tended to have greater reductions in depression at post-treatment, which is consistent with statistical principles (Vickers &

Altman, 2001). CGs who already report low depression at baseline have less room for further reducing their depression scores post-treatment.

Exploratory Analyses: Responders vs. Non-responders

Exploratory analyses investigated differences between responders vs. non-responders to PEP. It was found that CGs who had at least a 50% reduction in depression were providing care for a spouse that was significantly younger than spouses of CGs who were non-responders. However, no differences were found in the level of dependence of the care recipient. Moreover, there was a non-significant trend for depressive symptom responders to be younger than non-responders. CGs who had a 50% reduction in IL-6 scores had higher personal mastery at baseline. There was also a non-significant trend such that CGs in PEP who had 50% reduction in D-Dimer had higher self-reported overall health and provided a smaller number of hours of care per day. An important caveat to consider in interpreting these exploratory findings is that unequal group sizes may have impacted the detection of statistically significant differences. Notably, as exploratory analyses divided CGs in the PEP condition into two groups, test statistics may be biased by small and unequal sample sizes.

Strengths & Limitations

Strengths from the current study include utilization of multiple imputation to directly address missing data and exploratory analyses to identify factors that may predict a treatment response (defined as 50% reduction or more in depression or IL-6 scores). A major limitation in the current study is the fact that a smaller sample size may have reduced power in detecting mediators and moderators of depression changes after PEP. Additionally, the original PEP efficacy study did not utilize oversampling methods to

increase variance of potential moderators and mediators. Moreover, findings from the current study may not necessarily generalize to a wider population of CGs, as the current sample lacked ethnic and socioeconomic diversity.

Conclusions

Findings from the current study suggest that CGs who have higher depression will derive greater benefit from interventions, irrespective of receiving a pleasant activities behavioral activation intervention or supportive intervention. Moderators of differential treatment response to a behavioral activation treatment vs supportive therapy treatment in CGs are still unknown. Working status, social support, CG vulnerability, and disruptive behaviors did not significantly alter CGs' response to PEP vs. IS. Moreover, explanatory mechanisms that account for changes in CG depression after PEP are still unknown. Although it was hypothesized that activity restriction change, frequency of pleasant events change, and personal mastery change may account for changes in depression after PEP, these were non-significant in the current study. Future studies may explore acceptance and positive reappraisal as potential mediators of intervention outcomes.

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Tables and Figures

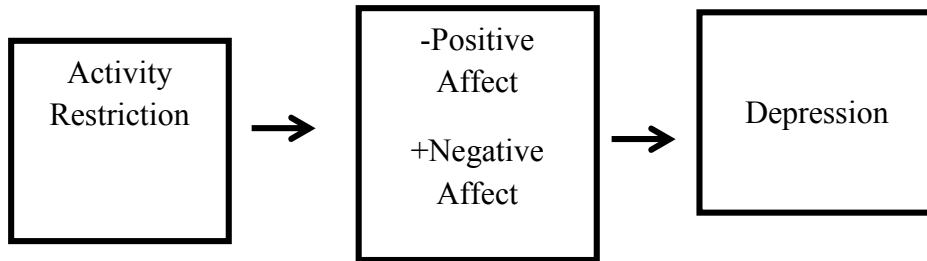


Figure 1: *Activity Restriction Model of Depressed Affect (Williamson & Shaffer, 2000)*

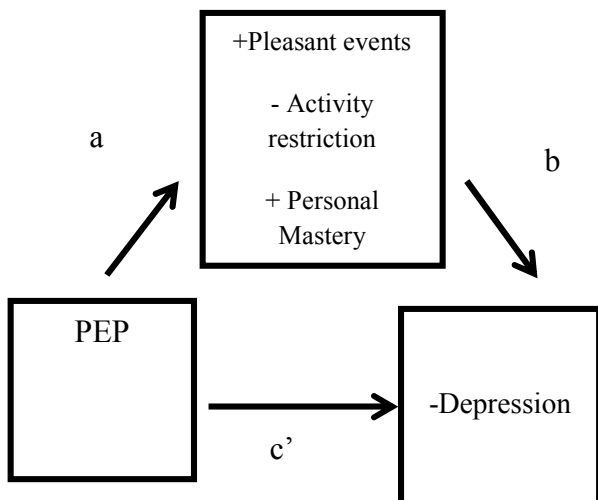


Figure 2a: *Mediators of PEP on Depression*

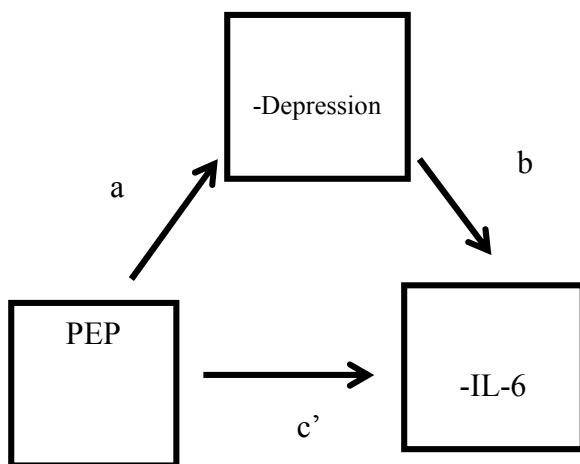


Figure 2b: *Mediator of PEP on CVD risk*

Note: PEP = Pleasant Events Program; IL-6 = Interleukin-6

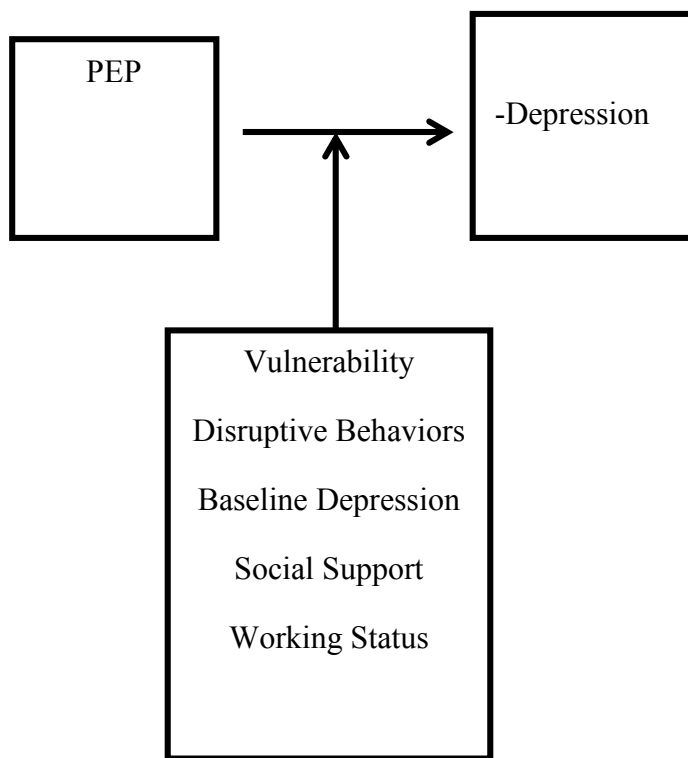


Figure 3: *Moderators of PEP on Depression and CVD Risk*

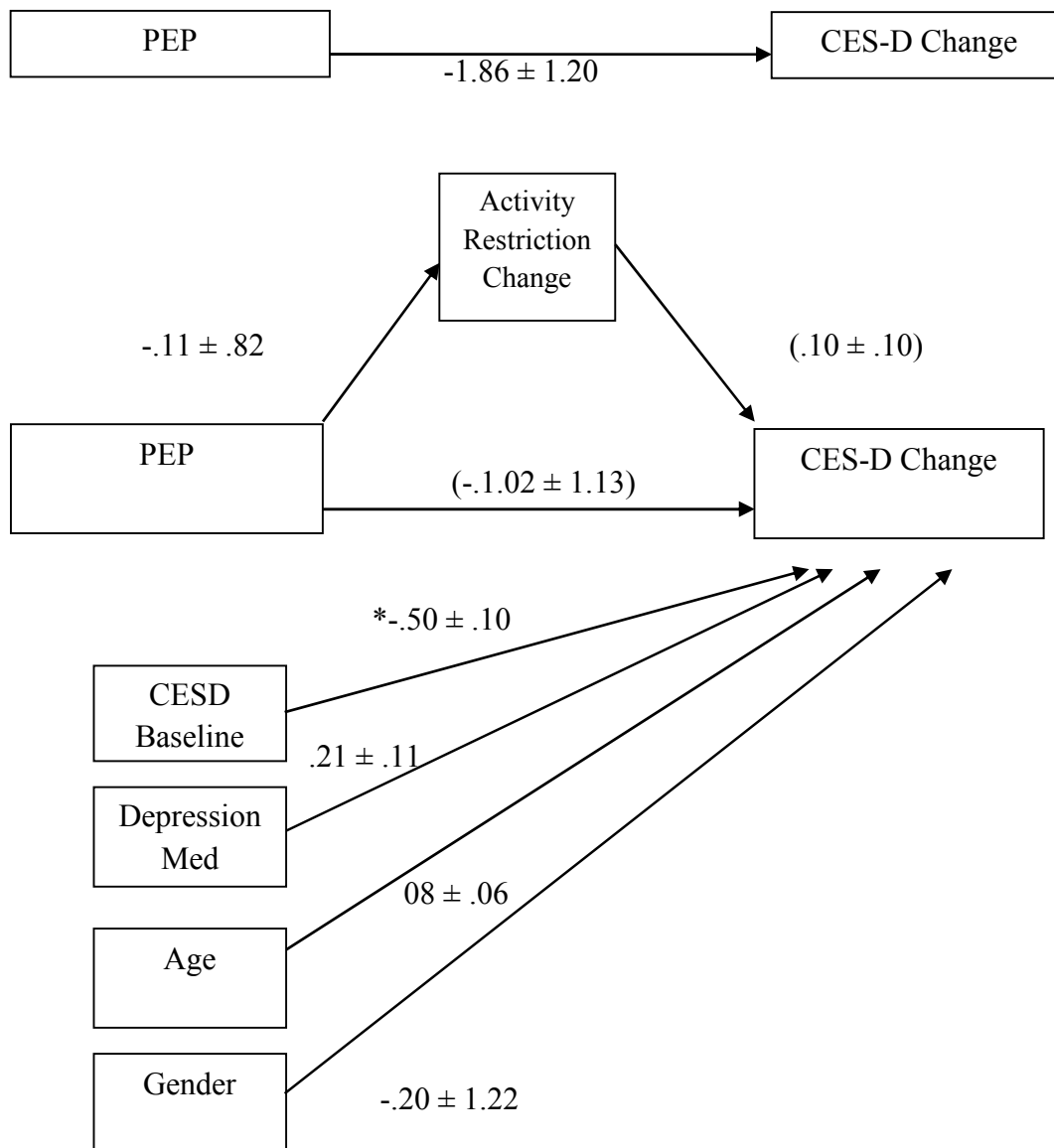


Figure 4: *Activity Restriction Mediation Model*

Note: Values depicted on paths are regression coefficients and their standard error: $B \pm SE$. Values in parentheses are partial regression coefficients when both PEP and mediators are included in the model. ** indicates $p < .01$ * indicates $p < .05$

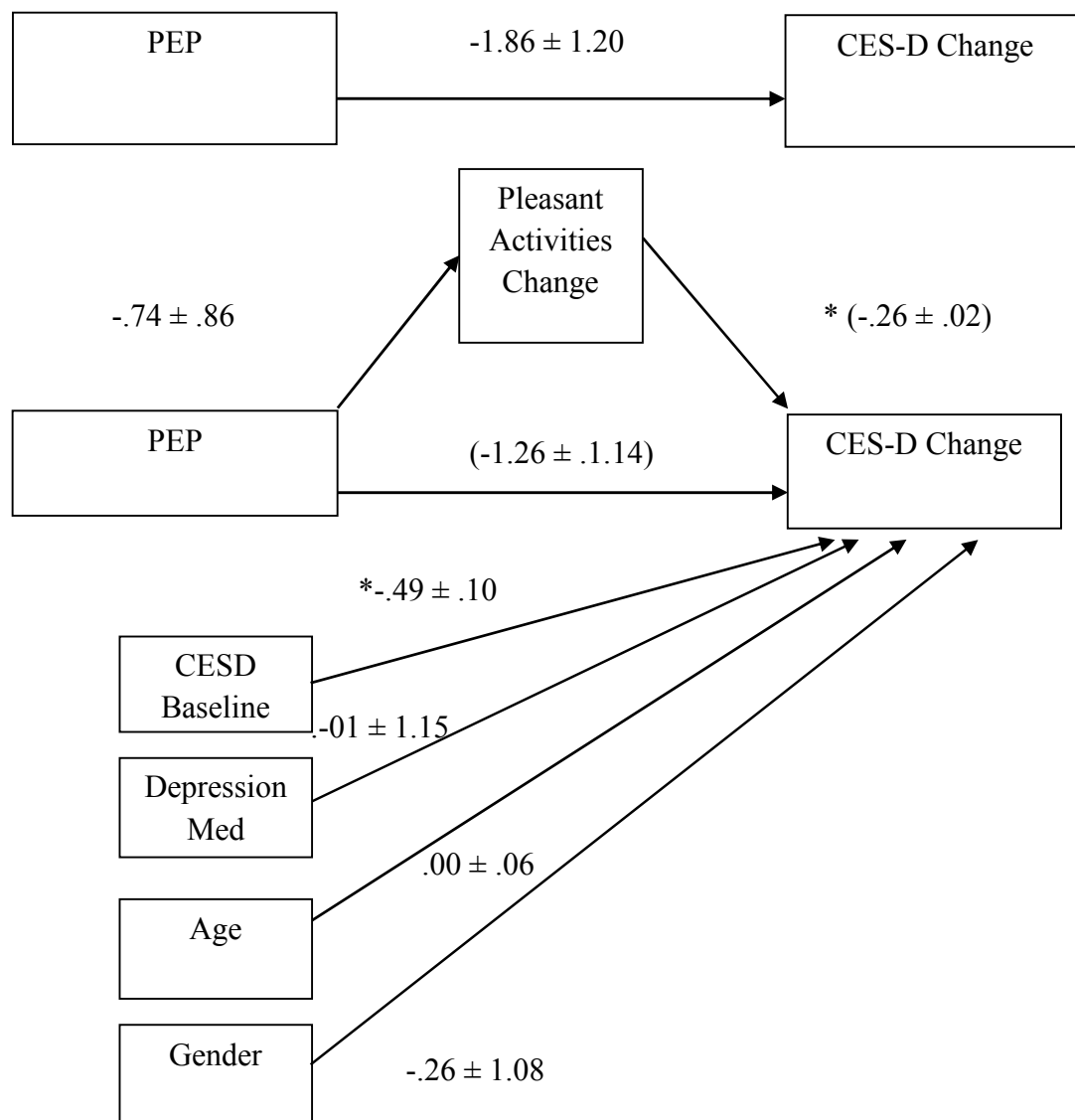


Figure 5: *Pleasant Activities Mediation Model*

Note: Values depicted on paths are regression coefficients and their standard error: $B \pm SE$. Values in parentheses are partial regression coefficients when both PEP and mediators are included in the model. ** indicates $p < .01$ * indicates $p < .05$

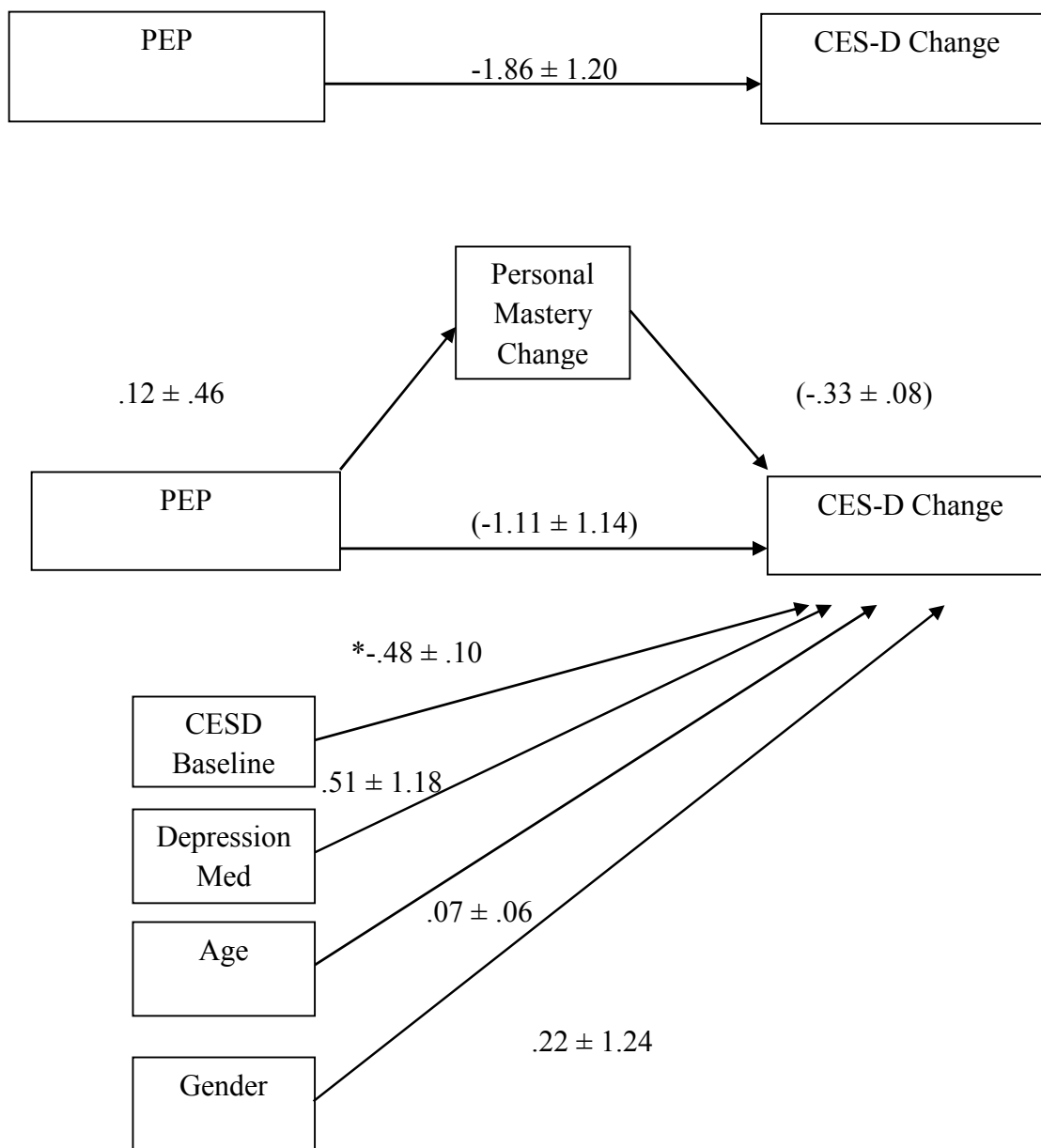


Figure 6: *Personal Mastery Mediation Model*

Note: Values depicted on paths are regression coefficients and their standard error: $B \pm SE$. Values in parentheses are partial regression coefficients when both PEP and mediators are included in the model. ** indicates $p < .01$ * indicates $p < .05$

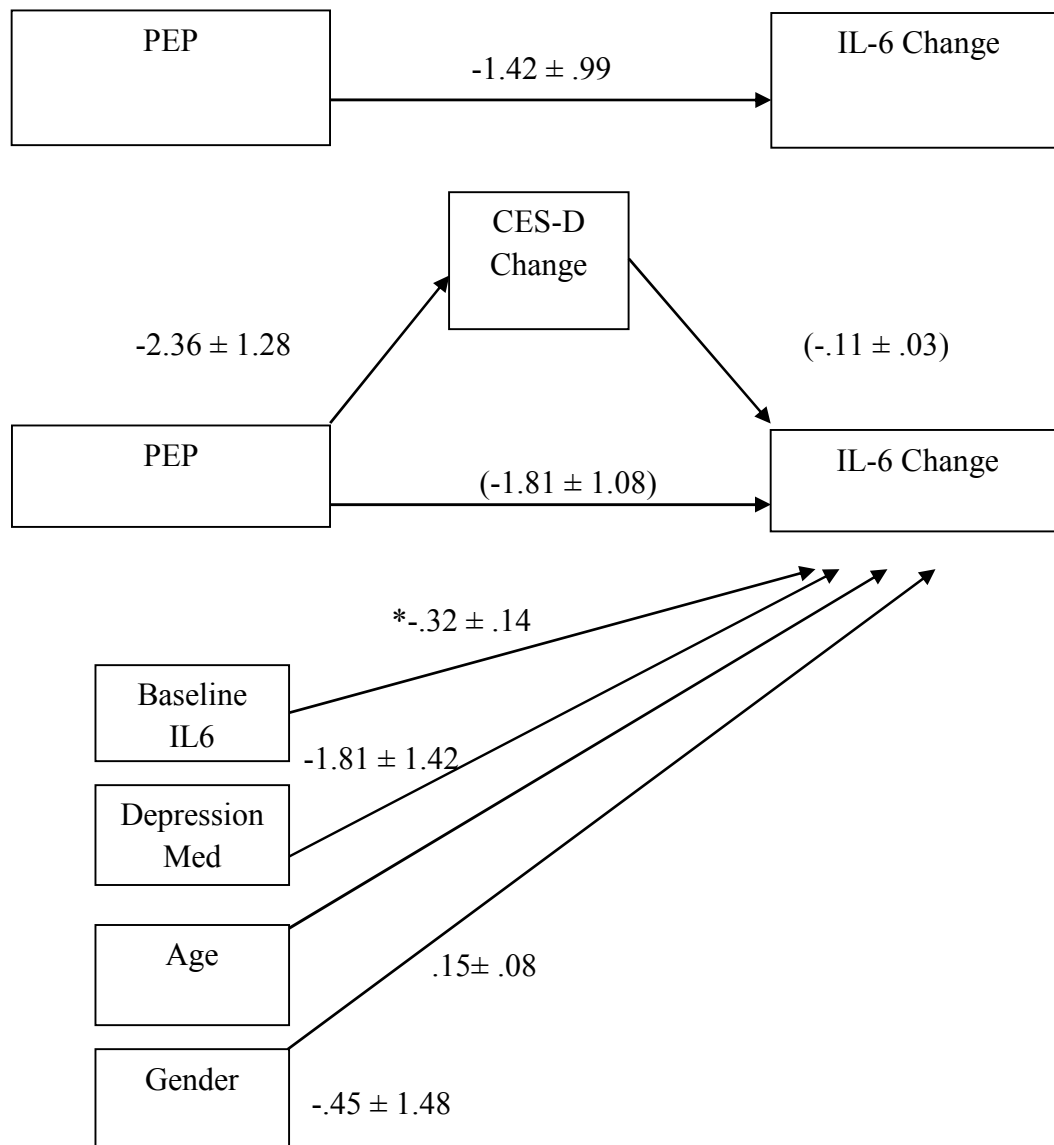


Figure 7: Mediators of Post-Treatment Changes in IL-6

Note: Values depicted on paths are regression coefficients and their standard error: $B \pm SE$. Values in parentheses are partial regression coefficients when both PEP and mediators are included in the model. ** indicates $p < .01$ * indicates $p < .05$. IL-6 unit = pg/mL

Table 1: *Data Used for Secondary Analysis*

	Baseline	6-week
Caregiver Demographics	X	
CES-D	X	X
D-Dimer	X	X
Interleukin-6	X	X
Use of Respite Services	X	
Disruptive Behaviors	X	
Vulnerability	X	X
Pleasant Events	X	X
Activity Restriction	X	X

Note: CES-D = Center for Epidemiologic Studies-Depression

Table 2: *Baseline characteristics of the sample by treatment condition*

	PEP (n = 48)	IS (n = 50)
Caregiver characteristics		
Age (years), mean (SD)	70.71 (7.57)	70.98 (8.81)
Sex (female), n (%)	40 (83.3)	34 (68.0)
Caucasian, n (%)	45 (93.8)	47 (94.0)
Education (years), mean (SD)	15.19 (2.28)	15.16 (3.46)
Years caregiving, mean (SD)	4.57 (1.19)	6.86 (3.89)
Taking anti-depressant medications, n (%)	18 (37.5%)	15 (30.0%)
Hours providing care per day, mean (SD)	8.19 (5.04)	8.14 (5.36)

Table 3: *Descriptive Statistics and Missing Values*

		Baseline					Post-Treatment				
		Missing		Valid N			Missing		Valid N		
		N	%				N	%			
IS	currently working (n, %)	5.0	9.8	46.0	23.0	46.0	-	-	-	-	-
	square root D-Dimer (M, SD)	6.0	11.8	45.0	25.6	6.3	14.0	27.5	37.0	24.3	5.3
	log IL-6 (M, SD)	5.0	9.8	46.0	0.3	0.8	8.0	15.7	43.0	0.1	0.4
	SOCIAL SUPPORT(M, SD)	0.0	0.0	51.0	25.4	4.2	-	-	-	-	-
	PROBLEM BEHAVIORS (M, SD)	0.0	0.0	51.0	24.4	7.2	-	-	-	-	-
	CES-D (M, SD)	0.0	0.0	51.0	10.9	5.5	0.0	0.0	51.0	9.7	5.3
	PERSONAL MASTERY (M, SD)	0.0	0.0	51.0	10.6	3.1	8.0	15.7	43.0	11.5	3.4
	Activity Restriction (M, SD)	0.0	0.0	51.0	17.7	5.9	9.0	17.6	42.0	17.6	6.3
	Pleasant Events (M, SD)	1.0	2.0	50.0	29.0	5.8	8.0	15.7	43.0	28.9	5.1
	ADL/IADL (M, SD)	0.0	0.0	51.0	10.1	3.5	-	-	-	-	-
PEP	currently working (n, %)	6.0	12.2	43.0	20.0	41.7	-	-	-	-	-
	square root D-Dimer (M, SD)	2.0	4.1	47.0	25.6	7.7	12.0	24.5	37.0	23.9	7.3
	log IL-6 (M, SD)	4.0	8.2	45.0	0.1	0.8	3.0	6.1	46.0	0.0	0.4
	SOCIAL SUPPORT(M, SD)	0.0	0.0	49.0	25.2	3.7	-	-	-	-	-
	PROBLEM BEHAVIORS (M, SD)	0.0	0.0	49.0	26.2	9.6	-	-	-	-	-
	CES-D (M, SD)	0.0	0.0	49.0	12.3	4.9	0.0	0.0	49.0	9.2	5.3
	PERSONAL MASTERY (M, SD)	0.0	0.0	49.0	10.9	2.6	6.0	12.2	43.0	11.7	2.7
	Activity Restriction (M, SD)	0.0	0.0	49.0	18.2	5.7	6.0	12.2	43.0	17.6	6.8
	Pleasant Events (M, SD)	0.0	0.0	49.0	29.5	5.2	6.0	12.2	43.0	27.8	5.7
	ADL/IADL (M, SD)	0.0	0.0	49.0	10.0	3.1	-	-	-	-	-

Note: means of variables with missing values reflect imputed values; IL-6 & D-Dimer units =pg/mL

Table 4: Regression Results Displaying Interaction Effects

		β	<i>SE</i>	<i>t</i>	<i>p</i>
Disruptive Behaviors	baseline CESD	-0.46	.11	-4.33	.00
	Treatment Group	-.58	3.84	-.15	.88
	Age	.07	.07	1.08	.28
	Gender	.14	1.30	.10	.92
	Depression Med	.36	1.25	.29	.78
	disruptive behaviors	.13	.11	1.18	.24
	group \times disruptive	-.03	.14	-.19	.85
Social Support	baseline CESD	-.46	.11	-4.33	.00
	Treatment Group	-1.35	8.20	-.17	.87
	Age	.06	.07	.85	.40
	Gender	.38	1.32	.29	.77
	Depression Med	.53	1.25	.43	.67
	social support	-.20	.19	-1.02	.31
	group \times social support	.01	.32	.04	.97
Working Status	baseline CESD	-.44	.10	-4.10	.00
	Treatment Group	-.56	1.65	-.34	.74
	Age	.06	.07	.89	.38
	Gender	.01	1.35	.01	.99
	Depression Med	.69	1.02	.67	.50
	Working status	.97	1.50	.64	.52
	group \times working	-.86	2.62	-.33	.75
Vulnerability	baseline CESD	-.47	.10	-4.53	.00
	Treatment Group	-.40	1.38	-.29	.77
	Age	.07	.07	1.13	.26
	Gender	.37	1.27	.29	.77
	Depression Med	.07	1.27	.06	.96
	Vulnerability	2.36	3.09	.76	.45
	group \times vulnerability	-6.98	4.59	-1.52	.13
Baseline CESD	baseline CESD	-.31	.14	-2.24	.03
	Treatment Group	2.36	2.75	.86	.39
	Age	.05	.07	.74	.46
	Gender	-.07	1.29	-.06	.96
	Depression Med	.46	1.27	.36	.72
	group \times baselineCESD	-.29	.22	-1.3	.19

Table 5a: *CES-D Treatment Response by Condition*

	Non-Responder	Responder
IS	44	6
PEP	32	16

Table 5b: *IL-6 Treatment Response by Condition*

	Non-Responder	Responder
IS	31	3
PEP	25	7

Table 5c: *D-Dimer Treatment Response by Condition*

	Non-Responder	Responder
IS	43	1
PEP	44	3

Note: Table displays number of non-responders vs. responders by treatment condition and treatment outcome. Note that a CG was considered to be a responder if there was at least a 50% reduction in treatment outcome scores

Appendix A

Center for Epidemiologic Studies Short Depression Scale (CES-D 10)

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way during the past week by checking the appropriate box for each question.

Items:	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)
1. I was bothered by things that usually don't bother me.				
2. I had trouble keeping my mind on what I was doing				
3. I felt depressed.				
4. I felt that everything I did was an effort.				
5. I felt hopeful about the future.				
6. I felt fearful.				
7. My sleep was restless.				
8. I was happy.				
9. I felt lonely.				
10. I could not "get going."				

Pleasant Events Schedule

Instructions: This schedule contains a list of events or activities that people sometimes enjoy. It is designed to find out about things your relative has enjoyed during the past month. Please rate each item twice. The first time, rate each item on how many times it happened in the past month, (frequency); the second time, rate each event on how much your relative enjoys the activity.

Activity	Frequency			Enjoy		
	Not at all	1 to 6 Times	7 or more Times	Not At All	Some what	A Great Deal
1. Being outside						
2. Shopping, buying things						
3. Reading or listening to stories, magazines, newspapers						
4. Listening to music						
5. Watching T.V.						
6. Laughing						
7. Having meals with friends or family						
8. Making or eating snacks						
9. Helping around the house						
10. Being with family						
11. Wearing favorite dothes						
12. Listening to the sounds of nature (birdsong, wind, surf)						
13. Getting/sending letters, cards						
14. Going on outings (to the park, a picnic, etc)						
15. Having coffee, tea, etc. with friends						
16. Being complimented						
17. Exercising (walking, dancing, etc.)						
18. Going for a ride in the car						
19. Grooming (wearing make up, shaving, having hair cut)						
20. Recalling and discussing past events						

Activity Restriction Scale

How much have you felt restricted from doing the following activities over the past month:

1. Caring for yourself
2. Caring for others
3. Doing household chores
4. Going shopping
5. Visiting friends
6. Working on hobbies
7. Sports and recreation
8. Going to work
9. Maintaining friendships

0	1	2	3	4
Never or seldom do this	Not restricted at all	Slightly restricted	Moderately restricted	Greatly restricted

Revised Memory and Behavior Checklist

Instructions: The following is a list of problems patients sometimes have. Please indicate if any of these problems have occurred during the past week. If so, how much has this bothered or upset you when it happened. Use the following scale for your reaction. Please read the description of the ratings carefully.

Has it occurred in the past week:

0 = No
1 = Yes

Reaction Ratings:

0 = not at all
1 = a little
2 = moderately
3 = very much
4 = extremely

Please answer all the questions for both frequency and reaction.

(RC11)

Problem	Has it occurred? (in past week)		Reaction (how much it bothered you)
	NO	YES	
1. Asking the same question over and over	NO	YES	
2. Trouble remembering recent events (i.e. items in newspaper or TV)	NO	YES	
3. Trouble remembering significant past events	NO	YES	
4. Losing or misplacing things	NO	YES	
5. Forgetting what day it is	NO	YES	
6. Starting, but not finishing, things	NO	YES	
7. Difficulty concentrating on a task	NO	YES	
8. Destroying property	NO	YES	
9. Doing things that embarrass you	NO	YES	
10. Waking you or other family members up at night	NO	YES	
11. Talking loudly and rapidly	NO	YES	
12. Appears anxious or worried	NO	YES	
13. Engaging in behavior that is potentially dangerous to self or others	NO	YES	
14. Threats to hurt oneself	NO	YES	
15. Threats to hurt others	NO	YES	
16. Aggressive to others verbally	NO	YES	
17. Appears sad or depressed	NO	YES	
18. Expressing feelings of hopelessness or sadness about the future	NO	YES	
19. Crying and tearfulness	NO	YES	
20. Commenting about death of self or others	NO	YES	
21. Talking about feeling lonely	NO	YES	
22. Comments about feeling worthless or being a burden to others	NO	YES	
23. Comments about feeling like a failure, or about not having any worthwhile accomplishments in life	NO	YES	
24. Arguing, irritability, and/or complaining	NO	YES	